(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 307 087 B1**

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **08.06.94**

(51) Int. Cl.5: **A61K 31/02**, A61K 9/107, A61K 47/24

(21) Application number: **88307233.2**

(22) Date of filing: **05.08.88**

(54) Fluorocarbon emulsions for in vivo use.

(30) Priority: **05.08.87 US 82846**

(43) Date of publication of application:
15.03.89 Bulletin 89/11

(45) Publication of the grant of the patent:
08.06.94 Bulletin 94/23

(84) Designated Contracting States:
AT BE DE ES FR GB IT LU NL SE

(56) References cited:
EP-A- 0 231 070
EP-A- 0 282 949
FR-A- 2 105 287
GB-A- 1 361 068
US-A- 3 958 014

PATENT ABSTRACTS OF JAPAN, vol. 10, no. 13 (C-323)[2070], 18 January 1986; p. 44 C 323&NUM;

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Description

The present invention relates to the art of non-toxic oxygen transport and contrast enhancement agents for internal and external animal use, and more particularly to stable high concentration fluorocarbon emulsions capable of sterilization and which are selectively free of calcium precipitation, reduce in vivo and in vitro red blood cell, or erythrocyte, injury, reduce anemia effects, and have reduced viscosity and reduced rate of oxidation or free radical damage, particularly of components of the emulsion and of contacted body tissue.

In the past, efforts to use emulsified fluorocarbons as an oxygen transport or carrier, as in a blood substitute, and as a contrast enhancement agent, as for X-ray, ultrasound and magnetic resonance imaging, having encountered certain difficulties. Purity, non-toxicity, chemical and biological inertness and ability to excrete are desirable objectives. The emulsified fluorocarbon must be capable of sterilization, preferably by heat, have long-term size and function stability preferably in the fluid state, be industrially feasible, persist for sufficiently long or effective times in the blood stream when used intravascularly and be eliminated sufficiently rapidly from the body.

For intravenous use, it is considered important to have small particle size. However, long term storage for extended periods of time for a month or longer, of blood substitutes has heretofore resulted in conglomeration or coalescence of the fluorocarbon particles in the emulsion into larger particles, especially after heat sterilization. For a general discussion of the objectives and a review of the efforts and problems in achieving these objectives in fluorocarbon blood substitutes, see "Reassessement of Criteria for the Selection of Perfluoro Chemicals for Second-Generation Blood Substitutes: Analysis of Structure/Property Relationship" by Jean G. Riess, 8 Artificial Organs, 34-56, (1984).

Larger particle sizes are dangerous in intravenous use in that they tend to collect in the lung, liver, spleen and some other organs, enlarging them and endangering their functioning. On the other hand, it is desired to have sufficient particle size in the fluorocarbon particles for them to collect in tumors and other areas when fluorocarbons are used as a contrast enhancement medium. Larger particle sizes within reasonable limits, also, are unobjectionable when used in other, non-venous systems in the body, such as, for example, the cerebrospinal fluid ventricles and cavities.

In the past, it has been observed that fluorocarbon emulsions used intravascularly accumulate disproportionately more in the spleen, as opposed to other organs such as the liver. This concentration in the spleen sometimes causes a transient hypersplenism, a condition characterized by an enlarged and over-active spleen from which a transient anemia results. A fluorocarbon emulsion having the above-indicated characteristics but also having a more even distribution among the major body organs is desired.

Glycerol is normally a good osmotic agent for fluorocarbon emulsions, but in concentrations has been observed to hemolize the red blood cells. The glycerol apparently swells the red blood cells, damaging the cells, promoting the egress of hemoglobin and thus causing damage to the cells. Certain other additives, notably sugars have similar red blood cell damaging effects. It has long been desired to avoid or to limit the amount of such hemolytic agents in the emulsion.

It is known that lecithin and other phospholipids are subject to oxidation in the vascular system. Such oxidation of lecithin phospholipids is also observable in respect to the lecithin phospholipid emulsifier components of stored or packaged fluorocarbon emulsions. It is desired to have effective, stable and non-toxic fluorocarbon emulsions having phospholipid emulsifying agents or other oxidizable components wherein oxidation is inhibited.

It is frequently desired to have high concentration fluorocarbon emulsions, but they unfortunately tend to have high viscosity. It may also be desired to have emulsions containing nutrients, such as glucose and like sugars. Glucose, however, has been known to make fluorocarbon emulsions more viscous. It is desired to have fluorocarbon emulsions that are less viscous and more fluidic, to facilitate packaging, injectability and avoidance of blood vessel blockage.

It has been desired, further, to provide a vehicle carrier for delivering fat or oil soluble and fluorocarbon soluble medicines through the intravascular, intraperitoneal, oral, respiratory, cerebrospinal and other internal animal body tissue or systems, including human tissue, as well as for delivering such medicines externally such as cutaneously through the skin. "Tissue" in this specification will be used to include blood.

It is often desirable to have some emulsions which contain or deliver calcium, and which do not have calcium precipitating components. Many buffers, however, are phosphates or carbonates and form excessive calcium precipitates which not only reduce the amount of calcium available for therapeutic use, but dangerously deposit calcium compounds in the tissue.

The present invention is directed toward improvements in the formulation and use of fluorocarbon emulsions to meet these and other objectives while providing a stable, non-toxic and efficacious fluorocar-

bon emulsion.

In brief, in accordance with one aspect of the invention, fluorocarbon emulsions having a concentration in the continuous phase of from 20% to 125% weight per volume is described whose mean particle size and particle distribution is maintained substantially stable through normal sterilization and storage procedures. The continuous phase of the emulsion shall be used herein to refer to the aqueous phase of the emulsion. In particular, for example, the term "weight per volume" or "w/v" will be used and should be understood to mean the ratio of the weight in grams per 100 cubic centimeters or 100 milliliters, or equivalent expressions or mathematical identities therof.

The fluorocarbon in emulsions may be mono-brominated perfluorocarbons, such as 1-bromoseptadecafluoroctane (C8F17Br, sometimes designated perfluoroctylbromide or "PFOB"), 1-bromopentadecafluoroseptane (C7F15Br), and 1-bromotridecafluorohexane (C6F13Br, sometimes known as perfluorohexylbromide or "PFHB"), C4F9CH-CHC4F9 ("F-44E"), i-C3F7CH-CHC6F13 ("F-i36E"), C6F13CH=CHC6F13 ("F-66E"), F-adamantane ("FA"), F-1,3-dimethyladamantane ("FDMA"), F-declin ("FDC"), F-4-methyloctahydroquinolidizine ("FMOQ"), F-4-methyldecahydroquinoline ("FHQ"), F-4-cyclohexylpyrrolidine ("FCHP"), F-2- butyltetrahydrofuran ("FC-75"), (CF3)2CFO(CF2CF2)2OCF(CF3)2, (CF3)2CFO(CF2CF2)3OCF(CF3)2, (CF3)2CFO(CF2CF2)2F, (CF3)2CFO(CF2CF2)3F, (C6F13)2O and F[CF-(CF3)CF2O]2CHFCF3.

The emulsion has for an emulsifying agent a phospholipid, an anionic surfactant, a fluorosurfactant or combinations thereof.

Osmolarity is maintained by an osmotic agent which has benefit independent of osmolarity, such as the hexahydric alcohols, namely mannitol and sorbitol which also are used to control viscosity and stabilize particle membrane structure. Other osmotic agents, such as certain sugars, namely glucose, mannose and fructose may be used which provide nutrition. Osmolarity is also affected by buffers, which are selected from imidazole or tris(hydroxymethyl)aminomethane, which do not precipitate calcium, or may be selected from such buffering agents as sodium chloride, sodium bicarbonate, magnesium chloride, monobasic potassium phosphate, dibasic potassium phosphate, calcium chloride, magnesium sulfate, monobasic sodium phosphate and dibasic sodium phosphate. Certain biocompatible combinations of these osmotic agents provide variously or inclusively for reduction of red blood cell injury in vivo and in vitro, for reduction of viscosity, for reduction in the rate of oxidation, for nutrition and for buffering the acidity or pH level. Tocopherol, mannitol, ascorbyl palmitate and imidazole may be added or increased to further reduce the rate of oxidation of the emulsion components in vitro, and also are believed to have similar effects in vivo to reduce the rate of oxidation of the body tissue or organ to which the emulsion may be applied.

A buffering agent maintains the pH at predetermined levels, and may provide osmotic pressure to maintain osmolarity. The buffering agents may include the non-calcium precipitating buffers imidazole, tris-(hydroxymethyl)aminomethane and other buffering agents such as sodium bicarbonate, monobasic potassium phosphate, dibasic potassium phosphate, monobasic sodium phosphate and dibasic sodium phosphate. Tris(hydroxy- methyl)aminomethane is sometimes called THAM, or by several of its trade names, such as, for example, Trizma by Sigma Chemical Company of St. Louis, Missouri.

The fluorocarbon emulsions are prepared, first by mixing in the aqueous or continuous phase the "vehicle" by adding osmotic agent(s), buffering agent(s), electrolytes if desired, emulsifying agent(s) and additional anti-oxidant(s) if desired. The fluorocarbon is mixed into the vehicle at a tempered rate so that the emulsion is tempered or homogeneous. The emulsion is then divided into separate flows which are impinged at high velocities upon each other in sheets in a cavity under relatively high pressure. The emulsions are then filtered, packaged, sterilized and otherwise processed for storage and use.

Other novel features which are believed to be characteristic of the invention, both as to organization and methods of operation, together with further objects and advantages thereof, will be better understood from the following description in which preferred embodiments of the invention are described by way of example.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

A fluorocarbon emulsion comprises a continuous, i.e. aqueous phase and a discontinuous phase. The discontinuous phase comprises the fluorocarbon with an emulsifying agent. Osmotic agents and biological pH buffers are included generally in the continuous phase to maintain osmolarity and pH.

The emulsifying agent generally surrounds and forms a layer around the discontinuous phase creating essentially fluorocarbon particles suspended within the continuous phase. Lecithin is used frequently as the emulsifying agent. Other emulsilfying agents may be used with good effect, such as fluorinated surfactants, also known as fluorosurfactants and anionic surfactants. Fluorosurfactants which will provide stable emulsions include triperfluoroalkylcholate [C7F15C(=O)O]3, perfluoroalkylcholestanol [C7F15C(=O)O], per-

fluoroalkyloxymethylcholate, XMO-10 and fluorinated polyhydroxylated surfactants, such as, for example, those discussed in "Design, Synthesis and Evaluation of Fluorocarbons and Surfactants for In Vivo Applications New Perfluoroalkylated Polyhydroxylated Surfactants" by J. G. Riess, et al. Such fluorosurfactants discussed therein include a fluorophilic tail, a hydrocarbon prolongator, a junction unit comprised of an ether, an ester or an amide, and a hydrophilic head. Fluorophilic tails include, for example, C3(CF2)n, where n equals from 4 to 10. XMO-10 is a fluorinated surfactant having a formula C3F7O(CF2)3C(=O)NH(CH2)3N-(=O)(CH3)2. To be an non-toxic fluorosurfactant, the fluorinated surfactant and the fluorocarbon should have an elimination rate from the animal body or organ such that the fluorocarbon and the fluorinated cosurfactant are eliminated from the body or organ before carcinosis, teratogenesis or embryotoxicity occurs. Suitable anionic surfactant which will provide a stable, non-toxic and biocompatible emulsion are polyoxyethylene-polyoxypropylene copolymers.

The osmolarity of normal, for example human tissue is approximately from 290 milliosmols to 300 milliosmols. Maintaining this osmolarity is important in preventing injury to cells, such as red blood cells and endothelial cells which line the blood vessels into which, for example, the emulsion may be injected. When the osmolarity is less than 290 milliosmols, down to 200 milliosmols, water tends to diffuse into the cells causing them to swell and sometimes burst. When the osmolarity is too high, on the order of greater than 700 milliosmols, the cells lose water and may shrink. Injection of hyperosmotic medicines often are painful and burn, and further may also cause clotting and obstruction of the veins. These complications may be prevented by controlling the osmolarity of the emulsion prior to administration.

Fluorocarbon emulsions with low osmolarity tend to show instability in coalescense of the discontinuous particles, especially when subjected to stress shelf life studies such as freeze and thaw cycles. Normally when the osmolarity is too high, on the order of greater than 650 milliosmols, the fluorocarbon emulsion particles tend to aggregate, which can lead to coalescence and separation of the emulsion. It has been found, however, that in formulating fluorocarbon emulsions, slight hyperosmolarity, in the range of from 300 milliosmols to approximately 450 milliosmols is favored in order (1) to protect more against freezing and thus to obtain more stability, and (2) to accommodate increased amounts of the osmotic and other active agents, especially where the osmotic agent has therapeutic and other beneficial effects, as will be explained more below.

In the preferred embodiment of the present invention, mannitol is added to the emulsion. It has been found that mannitol provides a means for maintaining osmolarity, for reducing red blood cell injury, for reducing viscosity, for providing anti-oxidant effects in the emulsion and for stabilizing the fluorocarbon particles. Because mannitol has such beneficial effects, greater amounts of mannitol can be tolerated in the body's tissues. When using mannitol as the osmotic agent, for example, the stability of the emulsion can be maintained at the desired osmolarity range of from 240 milliosmols to 650 milliosmols with from 0.25% weight per volume to 1.5% weight per volume. The body's tissues can tolerate substantially more mannitol for obtaining anti-oxidation effects, for emulsion stabilizing effects, for viscosity reducing effects and for red blood cell protection effects.

It is believed, further, that mannitol is responsible for an observed improvement in the distribution of the fluorocarbon emulsion particles among the major organs when applied within the animal body. The effects of mannitol are believed to reduce organ toxicity, which in turn is believed to largely account for the reduction of adverse anemia effects when using the emulsion.

It is believed that mannitol is incorporated into or interacts in some way with the lecithin or other emulsifier membrane of the fluorocarbon particle in emulsion, to form a more protective membrane. For lecithin, this interaction is believed to be a more competent cell barrier structure that is more renitent in the membrane. It is believed, further, that the mannitol does not adversely affect the stability of the particle size in the fluorocarbon emulsion, as will be discussed in greater detail below.

Additionally, the mannitol, it is believed, assists in forming a more competent and renitent cell barrier in the somewhat similar lecithin membrane barriers of red blood cells, thus protecting against injury to the red blood cell, which injury allows hemoglobin to escape. Reduction of red blood cell injury has been observed with mannitol added to the emulsion and both in vivo and in vitro experiments.

Glycerol has been used as an osmotic agent, but glycerol readily penetrates the red blood cell walls. This penetration causes swelling of the red blood cells allowing their hemoglobin to escape. The escape of hemoglobin results in red blood cell ghosts which cannot transport oxygen. This condition may contribute to observe transient anemia effects with high doses of fluorocarbon emulsions. Mannitol is preferred as the osmotic agent to glycerol where injury to red blood cells may be a problem.

Mannitol establishes an osmotic pressure in the continuous phase of the emulsion, and is preferred in the present invention as an osmotic agent. Mannitol, unlike other osmotic agents, such as, for examples, glucose, glycerol and saline, generally does not penetrate the red blood cell, and generally does not cause

the red blood cells to swell and be damaged. Swollen and damaged red blood cells allow hemoglobin to be released from the red blood cell, thus possibly contributing to the observed anemia effects.

The use of mannitol in the fluorocarbon emulsion, it is believed, reduces the temporary anemia effects sometimes observed during discrete time periods in animals after receiving exaggerated doses of perfluorocarbon emulsion. It is believed that the highly desired and long sought reduction in anemia effects is due to distribution equilibration of the fluorocarbon emulsion among the body organs by mannitol, and to reduction of red blood cell injury . This reduction in anemia effects has been observed in adolescent Sprague Dawley rats, as may be better seen in the following Examples I and II.

EXAMPLE I

Two grams per kilogram of body weight of a 100% weight per volume emulsion of perfluoroctylbromide were infused intravenously into twenty-two Sprague Dawley rats, some (ten) of the rats getting an emulsion having 0.6% weight per volume of mannitol while other rats (twelve) received an emulsion having no mannitol but having a saline concentration providing equivalent osmotic pressure. There were ten other control rats which received a placebo injection of physiologic saline in a dose of two milliliters per kilogram of body weight. The emulsion was further comprised of 6% weight per volume of lecithin, 0.0252% weight per volume of THAM. At two weeks, the rats receiving the emulsion including mannitol had in their red blood cells an average of 97% of hemoglobin (measured in grams/deciliter) as found in the control rats. The rats receiving the emulsion having no mannitol had at two weeks an average of 91% blood hemoglobin as compared to the control rats. The hemoglobin was measured by hemolyzing the red blood cells in the blood and measuring the amount of hemoglobin released.

EXAMPLE II

Rats of the same type as used in Example I were used in further tests, into which rats ten grams per kilogram of body weight of the emulsions as described for Example I above, were injected intravenously. At two weeks, the rats receiving the emulsion containing mannitol averaged 87% hemoglobin as compared with the control rats. The rats receiving the emulsion not having the mannitol averaged 70% hemoglobin at two weeks.

Mannitol thus was successful in reducing anemia effects even in rats receiving very high doses of fluorocarbon emulsions.

More significantly affecting these reductions in anemia effects, it is believed, is the observed difference in major body organ distribution resulting from using mannitol as an osmotic agent and as an emulsion stabilizer over other osmotic agents. As noted, it has been observed in the past that fluorocarbon emulsions accumulate more in the spleen, on the order of IO to 15 times more than in other organs such as the liver. It is believed that this high concentration of fluorocarbon emulsion particles in the spleen is caused by the macrophages engulfing the particles and trapping them in the spleen. This large accumulation is unnecessary for effective imaging and sometimes causes hypersplenism, a condition characterized by an enlarged and over-active spleen from which anemia may result. When using mannitol as the osmotic agent, this accumulation is significantly reduced, on the order of approximately forty-eight percent (48%) as may be appreciated from the following Example III. Thus, the risk of hypersplenism and accompanying anemia is believed to be significantly reduced. This more equilibrated distribution can be seen better from the following experiment given by way of example:

EXAMPLE III

A dose of the 100% weight per volume perfluoroctylbromide emulsion having 0.6% weight per volume of mannitol comprising one gram per kilogram of body weight was injected intravenously into adolescent Sprague Dawley rats, and the level of concentration of the perfluoroctylbromide in the spleen was measured at twenty-four hours. The concentration was measured at 30.1 ± 1.5 milligrams per gram of spleen tissue. A substantially comparable 100% emulsion not having mannitol has typically in the past resulted in, for example, 57.61 ± 2.345 milligrams per gram of spleen tissue for the same dose.

Other organs, such as the liver showed a slight increase in perfluoroctylbromide concentration when using the same mannitol containing emulsion. In the rats receiving the emulsion with mannitol, a concentration of 5.6 ± 0.14 mg/gm. liver tissue was observed, as compared with 4.605 ± 0.533 mg./gm. liver tissue in a typical IOO% emulsion not containing mannitol.

The anemia is very significantly and substantially reduced if not virtually eliminated altogether when mannitol is incorporated into the fluorocarbon emulsion.

Mannitol is, further, an anti-oxidant interacting with the free radicals in the body's systems generally, as well as with free radicals in stored emulsion. Further, it has been found that mannitol reduces the viscosity of the emulsion. With mannitol, reduced viscosity is observed in high concentration fluorocarbon emulsions and in fluorocarbon emulsions in which glucose or other nutrients have been added. As noted, glucose has been found to make fluorocarbon emulsions more viscous, but it has been observed that adding mannitol to such an emulsion restores viscosity to even less than the viscosity of an emulsion without glucose.

The anti-oxidation characteristics of the emulsion are improved dramatically by adding tocopherols, such as alpha tocopherol acetate, as may be seen from the results of experiments given in the following Example IV.

EXAMPLE IV

Fluorocarbon emulsions were prepared without mannitol or tocopherol (Batch I in the table 1 below), with mannitol but without tocopherol (Batch II in the table 1 below), with tocopherol but without mannitol (Batch III in the table 1 below) and with mannitol; and tocopherol together (Batch IV in the table 1 below). In Batch II, mannitol was added in the amount of 0.6% weight per volume in the emulsion. Batch III had 0.05% weight per volume in alpha tocopherol acetate added. Batch IV comprises 0.6% weight per volume of mannitol and 0.05% weight per volume of alpha tocopherol acetate. The emulsions were 100% weight per volume perfluoroctylbromide emulsions having as the emulsifying agent 4.5% weight per volume lecithin, and further having 0.0252% weight per volume of THAM as a buffer to maintain the pH before the experiment and storage at 7.6, having 0.2% weight per volume of glucose for osmolarity, having 0.025% weight per volume of calcium chloride (CaCl), having 0.005% weight per volume of magnesium sulfate (MgSO4), and having water (H2O) quantity sufficient to form the remainder of the emulsion.

All emulsions were saturated with oxygen at the time of preparation. Oxygenation was accomplished by sparging with 100% oxygen during the formulation of the emulsion. Additionally, twenty milliliters (ml) of the emulsion were placed in a 30 ml bottle having the head space filled with 100% oxygen. The bottle was sealed.

Thereafter, the oxygenated emulsions were then sterilized at 121 degrees Centrigrade for eight minutes by autoclaving. Measurements of the partial pressure of oxygen (p02), partial pressure of carbon dioxide (pCO2), and hydrogen ion concentration (pH) were taken at ten days and thirty days, where the atmospheric pressure varied during the measurements from 741 mm of mercury (Hg) to 746 mm Hg. Measurements were taken at 38 degrees Centrigrade. The results are given in table 1 below, where in the first column are given the partial pressures of oxygen (pO2), in the second column are given the partial pressures of carbon dioxide (pCO2) and in the third column are given the resultant pH. The tocopherol used was alpha tocopherol acetate in a concentration of 0.05 grams per 100 milliliters of emulsion. The mannitol was O.6 grams per milliliter of emulsion. Readings were taken at ten (10) days and thirty (30) days after preparation of the emulsion, and the emulsion was stored at 10 degrees Centrigrade. All measurements except for pH are given in millimeters of Hg.

TABLE 1

Batch	10 days			3O days		
	p02	pC02	pH	p02	pC02	pH
I	550.0	10.2	3.3	242.4	12.8	3.2
II	650.1	0.7	7.171	643.4	1.2	7.072
III	627.3	0.5	7.361	656.4	1.4	7.098
IV	738.3	O.25	7.436	664.6	0.94	7.191

Since the emulsion was saturated with water, approximately 47 mm Hg of the total 741 to 746 mm Hg pressure should be attributed to H20 vapor. The emulsion having no mannitol, tocopherol or any other effective anti-oxidant shows a significant reduction in oxygen content occurring, and an increase in CO2 content with a pronounced acidity. No such deleterious effect occurs with the addition of mannitol, tocopherol or both. It can be observed that with mannitol and tocopherol used together, the emulsion becomes super-saturated with oxygen at ten days. At other times, the saturation of oxygen remains very

high, close to full saturation at ten and at thirty days for emulsions with mannitol and/or tocopherol added, with time having some effect.

As noted hereinabove, mannitol does not decrease the stability of the particle sizes in the emulsion. It is believed that mannitol actually improves the particle size stability by forming a protective interaction with the lecithin membrane to protect the fluorocarbon particles and prevent the particles from coalescing.

It has also been found that glucose is an effective osmotic agent and works well in fluorocarbon emulsions. The particle size characteristics of the emulsions are not degraded with glucose being used as an osmotic agent, it has also been found. Other sugars, such as mannose and fructose are effective osmotic agents, and are also metabolized in cells of the body to provide sources of energy. It is often desired, further, to have glucose in the emulsion as a nutrient.

It is believed that glucose, like mannitol, interacts with, or is incorporated in the lecithin membrane of the fluorocarbon particles to protect or stabilize the fluorocarbon particle membrane. This protection is particularly effective in freeze - thaw cycle accelerated shelf life studies. In such studies, it has been found that the particle size means remained substantially the same through as many as five rapid freezes to minus 20 degrees Centigrade, each followed by thawing at room temperatures.

The most common buffering agents normally include phosphate compounds. It is frequently desired, however, to include calcium containing compounds in the emulsion as an additional electrolyte and as a nutrient, in particular when perfusing the heart and the cerebro-ventricular systems. Calcium is essential, for example, for the heart muscle to contract. Calcium containing compounds, however, such as calcium chloride (CaCl) will form calcium precipitates with phosphate and carbonate buffers. Excessive amounts of such precipitates are harmful in the vascular and some other body systems, in that calcium precipitates block vessels. In this specification, the term "non-calcium precipitating" will be used to designate a mixture of solution which has substantially no calcium precipitates or has calcium precipitates in such small quantity so as not to result in undesired or harmful body reactions.

The hydrogen ion concentration (pH) of fluorocarbon emulsions is related to the emulsion stability and biological tolerance. Acidic pH reduces the electronegativity of the particles, which encourages aggregation and sedimentation. Alkaline pH tends to stabilize the emulsion by increasing electronegativity. Alkaline emulsions with a pH of up to 8.2 are well tolerated when injected into the coronary arteries. When the pH is less than 7.0, the emulsion may cause decreased contractility of the heart muscle and ventricular fibrillation. For intracoronary use, the pH should be from 7.0 to 7.8. An emulsion with a pH of between 4.0 and 8.4 can be used intravenously and in certain other arteries such as the femoral artery depending upon the purpose of the use.

Tris(hydroxymethyl)aminomethane, sometimes called THAM, is an effective buffering agent for fluorocarbon emulsions to maintain the pH at predetermined levels. THAM, also, in non-calcium precipitating; that is to say, THAM does not precipitate calcium salts.

It has also been found that imidazole is a very effective buffering agent for use in fluorocarbon emulsions. Imidazole is, also, non-calcium precipitating.

Both THAM and imidazole have an effect on the osmolarity of the emulsion. Use of imidazole or THAM increases the alkalinity of the emulsion, and normally would be used in conjunction with other osmotic agents to maintain the osmolarity without causing the pH to vary beyond desired levels.

If calcium is not desired or if moderate amounts of calcium precipitates can be tolerated, phosphate and carbonate buffers, including monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, dibasic potassium phosphate, sodium bicarbonate and combinations including these buffers will be suitable.

The osmotic agent and buffers discussed herein are effective for formulating several stable, non-toxic and/or efficacious fluorocarbon emulsions. For a stable emulsion, the fluorocarbon in emulsion may be mono-brominated perfluorocarbons, such as 1-bromoseptadecafluoroctane (C8F17Br, sometimes designated perfluoroctylbromide or "PFOB"), 1-bromopentadecafluoroseptane (C7F15Br), and 1-bromotridecafluorohexane (C6F13Br, sometimes known as perfluorohexylbromide or "PFHB"). Other stable fluorocarbon emulsions are C4F9CH-CHC4F9 (sometimes designated "F-44E"), i-C3F7CH-CHC6F13 ("F-i36E"), and C6F13CH=CHC6F13 ("F-66E"), C10F18 ("F-declin"), F-adamantane ("FA"), F-methyladamantane ("FMA"), F-1,3-dimethyladamantane ("FDMA"), F-declin ("FDC"), F-4-methyloctahydroquinolidizine ("FMOQ"), F-4-methyldecahydroquinoline ("FHQ"), F-4-cyclohexylpyrrolidine ("FCHP"), F-2-butyltetrahydrofuran ("FC-75"). Additional stable fluorocarbon emulsions that can achieve small particle sizes and long shelf lives when made in accordance with this invention include (CF3)2CFO(CF2CF2)2OCF(CF3)2, (CF3)2CFO(CF2CF2)3OCF(CF3)2, (CF3)2CFO(CF2CF2)2F, (CF3)2CFO(CF2CF2)3F, (C6F13)2O and F[CF-(CF3)CF2O]2CHFCF3. With the proviso that when the fluorocarbon is a brominated perfluorocarbon, the osmotic agent does not consist of a combination of sodium phosphates and glycerol. The present invention

as it relates to the aspects of such fluorocarbon emulsion stability can be further understood by reference to the following illustrative examples.

EXAMPLE V

An emulsion of F-44E, that is C4F9CH-CHC4F9, was prepared by first preparing an aqueous phase. The aqueous phase was in a solution containing 2.08% weight per volume of mannitol, 18.75% weight per volume of lecithin, and 0.104 weight per volume of alpha tocopherol acetate.

The aqueous phase was buffered with 0.0515% weight per volume THAM, resulting in a pH of approximately 7.8 after the emulsion was prepared for further testing. In order to arrive at this pH, the initial pH after adding the buffer was approximately 8.2. This buffered, aqueous phase solution is sometimes designated the vehicle. The vehicle is homogenized or mixed.

The fluorocarbon F-44E was then metered in a predetermined, measured rate into the vehicle or aqueous phase to ultimately achieve 86.1% weight per volume of the F-44E in the emulsion. The resulting amounts of the emulsion components were 9% weight per volume of lecithin, 1% weight per volume of mannitol, 0.05% weight per volume of tocopherol, 0.0247% weight per volume of THAM, and 100% weight per volume of F-44E.

The resulting mixture was then placed into a flow path which was divided into a plurality of flow paths. The flows were redirected to impinge upon each other at velocities in excess of 1500 feet per second in sheets of interaction in a cavity under 4,000 pounds per square inch or more of pressure and subjected to an ice bath kept at from five degrees to eight degrees Centrigrade surrounding the chamber containing the cavity. This flow procedure was repeated six times.

The emulsion was then sterilized by autoclave at 121 degrees Centigrade for eight minutes. The particle size distribution was analyzed in a Nicomp submicron particle sizer manufactured by Pacific Scientific Co. of Anaheim, California. This analyzer determines relative quantities of various sized particles by a method of dynamic light scattering. The fluorocarbon particles in the emulsion had a size characteristic of 188.1 nanometers mean diameter after this initial heat step.

The emulsion was then alternately frozen to minus 20 degrees Centrigrade and thawed to room temperature three times. The main fluorocarbon particle size measured after the third thaw was 193.8 nanometers. The emulsion was then subjected to three heat stress sessions of 121 degrees Centigrade for sixty minutes each. The particle size was then analyzed and found to have a characteristic mean diameter of 6O1.2 nanometers.

EXAMPLE VI

An emulsion of F-declin, that is C1OF18, was prepared by first preparing an aqueous phase. The aqueous phase was in solution containing 2.08% weight per volume of mannitol as an osmotic agent, 18.75% weight per volume of lecithin, and 0.104 weight per volume of alpha tocopherol acetate.

The aqueous phase was buffered with O.O515% weight per volume THAM, resulting in a pH approximately 7.8 after the emulsion was prepared for further testing. In order to arrive at this pH, the initial pH after adding the buffer was approximately 8.2. This buffered, aqueous phase solution is sometimes designated the vehicle. The vehicle is homogenized or mixed.

The fluorocarbon F-declin was then metered at a predetermined, measured rate into the vehicle or aqueous phase to ultimately achieve 99.53% weight per volume of the F-declin in the emulsion. The resulting amounts of the emulsion components were 9% weight per volume of lecithin, 1% weight per volume of mannitol, 0.05% weight per volume of tocopherol, 0.0247% weight per volume of THAM, and 100% weight per volume of F-declin.

The resulting mixture was then placed into a flow path which was divided into a plurality of flow paths. The flows were redirected to impinge upon each other at velocities in excess of 15OO feet per second in sheets of interaction in a cavity under 4,00O pounds per square inch or more of pressure and subjected to an ice bath as described for Example V above. This flow procedure was repeated six times.

The emulsion was then sterilized by autoclave at 121 degrees Centigrade for eight minutes. The particle size distribution was analyzed in the same Nicomp submicron particle sizer described above in Example V. The fluorocarbon particles in the emulsion had a size characteristic of 125.7 nanometers mean diameter after this initial heat step.

The emulsion was then alternately frozen to minus 20 degrees Centigrade and thawed to room temperature three times. The mean fluorocarbon particle size measured after the third thaw was 145.1 nanometers. The emulsion was then subjected to three heat stress sessions of 121 degrees Centigrade for

sixty minutes each. The particle size was then analyzed and found to have a characteristic mean diameter of 86.9 nanometers.

It has been found that, in general, it is desirable to repeat the flow and impingement steps for four times, and sometimes five and six times in order to maximize stability of the emulsion. Sometimes the heat generated by the impingement has a tendency to hydrolyze lecithin. This hydrolysis can be reduced or eliminated by maintaining the cavity in which the impingement takes places in an ice bath at approximately five to ten degrees Centigrade. It should be unnecessary to cool or otherwise remove heat from the impingement cavity when an emulsifying agent which is not heat sensitive is used. Many of the fluorinated surfactants are not heat sensitive, such as triperfluoralkylchlolate and perfluoroalkylcholestanol for examples.

Fluorocarbon emulsions can be used effectively for delivery of therapeutic agents, medicines and drugs throughout the body, tissue and organs. The particles comprising the discontinuous fluorocarbon phase of the emulsion comprise two principal components, the fluorocarbon and the encasing membrane. The stability of this discontinuous fluorocarbon phase allows at least two modes of carrying the therapeutic agent, medicine or drug, namely solution of the agent, medicine or drug within the fluorocarbon phase, and complexing of the agent, medicine or drug with the membrane. Examples of medicines, drugs and therapeutic agents which dissolve in the fluorocarbon are diazepam, cyclosporin, rifampin, clindamycin, isoflurane, halothane and enflurane. Examples of medicines, therapeutic agents and drugs which do not dissolve in fluorocarbon, but which complex with, for example, a lecithin membrane include mannitol, tocopherol, streptokinase, dexamethasone, prostaglandin E, Interleukin II, gentamycin and cefoxitin. Antibiotics may be delivered transcutaneously through the skin when added to a fluorocarbon emulsion.

Thrombolytic agents, such as streptokinase and other enzymes have been transported and delivered by fluorocarbon emulsions. It is believed that the low surface tension of the fluorocarbons, and of the fluorocarbon emulsions having lecithin or fluorosurfactants as the emulsifying agent, provide a very effective wetting fluid that permeates capillaries and vascular channels, as well as other narrow channels within the body. Transport of thrombolytic agents carried by such a fluorocarbon emulsion is demonstrated by the following Example VII:

EXAMPLE VII

A 40% weight per volume perfluoroctylbromide emulsion was prepared using the method described hereinabove in Example V, having 6% weight per volume lecithin as the emulsifying agent, 0.01% weight per volume dexamethasone, 0.01% weight per volume tocopherol, 1.5% weight per volume glycerol, and having as a buffer monobasic sodium phosphate at 0.012% w/v and dibasic sodium phosphate at 0.0563% w/v. The emulsion was formulated with the dexamethasone added during the vehicle formation. Streptokinase was added before the impingement flow steps, and three flow steps were performed.

The emulsion was placed in test tubes having clotted human blood. From 80% to 90% of the clots lysed in less than twenty minutes. Streptokinase alone, not in the presence of the fluorocarbon emulsion lyses the clots at substantially the same rate. Fluorocarbon emulsions, therefore, do not inhibit the action of the streptokinase.

The foregoing detailed description of my invention and of preferred embodiments, as to products, compositions and processes, as illustrative of specific embodiments only. It is to be understood, however, that additional embodiments may be perceived by those skilled in the art.

Claims

Claims for the following Contracting States : BE, DE, FR, GB, IT, LU, NL, SE

1. A fluorocarbon emulsion which is stable after heat sterilization and has a continuous aqueous phase, a discontinuous phase comprising a perfluorocarbon (other than a brominated perfluorocarbon) in emulsion in an amount of from 50% W/V to 125% W/V, an emulsifying agent and osmotic agent means, but not a combination of a phospholipid and a glyceride of fatty acids.

2. A biocompatible fluorocarbon emulsion for application to animal bodies and organs thereof, comprising a continuous aqueous phase, a discontinuous phase comprising a fluorocarbon in emulsion in an amount of from 50% weight per volume to 125% weight per volume, an emulsifying agent and one or more osmotic agent means for maintaining the osmolarity of the emulsion comprising an effective amount of a hexahydric alcohol, a sugar, sodium chloride, sodium bicarbonate, potassium phosphate, calcium chloride, magnesium chloride, magnesium sulphate, imidazole, tris(hydroxymethyl)-aminomethane, monobasic sodium phosphate or dibasic sodium phosphate or a biocompatible, non-

calcium precipitating combination thereof, the emulsion not comprising a combination of phospholipid and glyceride of fatty acids; with the proviso that when the fluorocarbon is a brominated perfluorocarbon the osmotic agent means does not consist of a combination of sodium phosphates and glycerol.

3. A fluorocarbon emulsion according to claim 1 or claim 2 wherein the osmotic agent means included a hexahydric alcohol.

4. A fluorocarbon emulsion as claimed in claim 1,2 or 3 wherein the emulsifying agent comprises a phospholipid, such as lecithin, and/or an anionic surfactant.

5. A fluorocarbon emulsion as claimed in any one of claims 1-4, wherein the fluorocarbon is selected from a mono-brominated per fluorocarbon, such as 1-bromoseptadeca-fluoroctane, 1-bromotridecafluorohexane or 1-bromo-pentadecafluoroseptane, C4F9CH-CHC4F9 and F-decalin.

6. A fluorocarbon emulsion as claimed in any one of claims 1 to 5, wherein the emulsifying agent comprises a biocompatible fluorinated surfactant.

7. A fluorocarbon emulsion as claimed in claim 6 wherein the fluorinated cosurfactant comprises a fluorinated polyhydroxylated surfactant.

8. A fluorocarbon emulsion as claimed in any one of claims 1 to 7 further comprising a buffering agent comprising imidazole and/or tris(hydroxymethyl)aminomethane.

9. A fluorocarbon emulsion as claimed in Claim 8 wherein the buffering agent group further comprises sodium bicarbonate, monobasic sodium phosphate, dibasic sodium phosphate, magnesium sulphate, magnesium chloride, sodium chloride, potassium chloride, monobasic potassium phosphate or dibasic potassium phosphate or a non-calcium precipitating combination thereof.

10. A fluorocarbon emulsion as claimed in any one of claims 1 to 9, wherein the pH of the emulsion is maintained at from 4.0 to 8.4, preferably from 7.0 to 7.8.

11. A fluorocarbon emulsion as claimed in claim 8 wherein said buffering agent is imidazole and the osmolarity of the emulsion is maintained at from 240 milliosmols to 650 milliosmols.

12. A fluorocarbon emulsion as claimed in any one of claims 2 to 11, wherein the hexahydric alcohol osmotic agent comprises mannitol.

13. A fluorocarbon emulsion as claimed in claim 11 suitable for application to tissue of animal bodies and/or organs thereof wherein the mannitol added to the emulsion is in the range of from 0.25 grams to 1.5 grams of mannitol per 100 millilitres of emulsion.

14. A fluorocarbon emulsion as claimed in any one of claims 1 to 13, which comprises an anti-oxidant.

15. A fluorocarbon emulsion as claimed in claim 14, wherein the anti-oxidant comprises mannitol, a tocopherol such as alpha-tocopherol acetate, ascorbyl palmitate and/or imidazole.

16. A fluorocarbon emulsion as claimed in claim 14 or 15, wherein the antioxidant comprises ascorbic acid, a salt or complex thereof or a non-calcium precipitating combination thereof.

17. A fluorocarbon emulsion as claimed in any one of claims 1 to 16, wherein the fluorocarbon in emulsion is in an amount of from 80% weight per volume to 125% weight per volume.

18. A fluorocarbon emulsion as claimed in any one of the claims 1 to 17, wherein the means for maintaining the osmolarity comprises mannitol, and the osmolarity of the emulsion is maintained at from 240 milliosmols to 650 milliosmols.

19. A fluorocarbon emulsion as claimed in claim 2, wherein the osmotic agent means includes at least a sugar.

20. A fluorocarbon emulsion as claimed in claim 19, wherein the sugar comprises glucose, mannose and/or fructose.

21. A fluorocarbon emulsion as claimed in claim 2, 19 or 20, wherein said osmotic agent means further includes mannitol and said sugar in an effective amount to reduce injury to red blood cells in vitro.

22. A fluorocarbon emulsion for application to animal bodies and organs thereof, comprising a continuous aqueous phase, 50% to 125% weight per volume of a fluorocarbon and an emulsifying agent and osmotic agent means for maintaining the osmolarity of the emulsion in the animal body and organs thereof but not a combination of phospholipid and glyceride of fatty acids, wherein the osmotic agent means is characterised by any of the following:
(a) non-glycerol and non-saline;
(b) non-calcium precipitating and suitable for maintaining the pH of the emulsion;
(c) non-saline, non-phosphate and non-glycerol and suitable for maintaining the pH of the emulsion.

23. A method for preparing a fluorocarbon emulsion substantially stable after sterilization and having from 50% weight per volume to 125% weight per volume of fluorocarbon in emulsion, comprising the steps of:
(a) preparing an aqueous phase vehicle by mixing in a sufficient quantity of water, an emulsifying agent, an effective amount of an osmotic agent;
(b) mixing into the vehicle at a measured rate a fluorocarbon to form a mixture;
(c) flowing the said resulting mixture into at least two flow paths;
(d) impinging the said flow paths of the mixture into each other in a cavity under greater than atmospheric pressure;
the emulsion not comprising a combination of phospholipid and glyceride of fatty acids, and with the proviso that when the fluorocarbon is a brominated fluorocarbon the osmotic agent means does not consist of a combination of sodium phosphates and glycerol.

24. A method as claimed in claim 23, wherein the vehicle further comprises a buffering agent comprising imidazole and/or tris(hydroxymethyl)aminomethane.

25. A method as claimed in claim 23 or 24, wherein the emulsifying agent comprises lecithin, a fluorinated surfactant or an anionic surfactant.

26. A method as claimed in claim 23,24 or 25, wherein the mixture is made to flow at 1500 feet per second (460 m/s) in the flowing step (c).

27. A method as claimed in any one of claims 23 to 26 wherein the cavity is maintained at 4000 pounds per square inch (28 MN/m^2), and/or the cavity has heat removed, for example by subjecting the cavity to an ice bath, preferably maintained at 5 °C, in the impinging step (d).

28. A method as claimed in any one of claims 23 to 27 wherein the flowing step and the impinging step are repeated, for example four times.

29. A method as claimed in claim 28, further including the steps of collecting the mixture after said impinging step, and sterilizing said mixture by autoclave.

30. A method as claimed in any one of claims 23 to 29, wherein in the vehicle, the osmotic agent, which is preferably non-calcium precipitating, includes a hexahydric alcohol, such as mannitol.

31. A method as claimed in any one of claims 23 to 30 wherein the fluorocarbon is selected from a monobrominated perfluorocarbon (such as 1-bromoseptadecafluoroctane, 1-bromopentadecafluoroseptane or 1-bromotridecafluoro-hexane), C4F9CH-CHC4F9, i-C3F7CH-CHC6F13, C6F13CH = CHC6F13, F-adamantane, F-1, 3-dimethyladamantane, F-decalin, F-4-methyloctahydroquinolidizine, F-4-methyldecahydroquinoline, F-4-cyclohexyl-pyrrolidine, F-2-butyltetrahydrofuran, (CF3)2CFO(CF2CF2)20CF-(CF3)2, (CF3)2CFO(CF2CF2)30CF(CF3)2, (CF3)2CFO(CF2CF2)2F, (CF3)2CFO(CF2CF2)3F, (C6F13)-20,F[CF(CF3)CF20]2CHFCF3 and a stable, compatible combination thereof.

32. The use of a fluorocarbon emulsion having a continuous phase, a discontinuous phase and a minor amount of an emulsifying agent forming a membrane between the two phases in the preparation of a delivery system for delivering a therapeutic drug into an animal body or an organ thereof.

33. The use as claimed in claim 32, wherein the drug is soluble in the fluorocarbon discontinuous phase or complexed with the membrane formed by the emulsifying agent.

34. The use as claimed in claim 32 or 33 emulsifying agent is lecithin and said drug is lipophilic.

35. The use as claimed in claim 32,33 or 34, wherein the drug is an enzyme, such as streptokinase, an antibiotic, such as cefoxitin, gentamycin, clindamycin and rifampin, a hematopoietic protector, such as imidazole or a derivative thereof, an anti-oxidant, such as mannitol, tocopherols or ascorbyl palmitate, or a thrombolytic enzyme.

Claims for the following Contracting State : AT

1. A fluorocarbon emulsion which is stable after heat sterilization and has a continuous aqueous phase, a discontinuous phase comprising a perfluorocarbon (other than a brominated perfluorocarbon) in emulsion in an amount of from 50% W/V to 125% W/V, an emulsifying agent and osmotic agent means.

2. A biocompatible fluorocarbon emulsion for application to animal bodies and organs thereof, comprising a continuous aqueous phase, a discontinuous phase comprising a fluorocarbon in emulsion in an amount of from 50% weight per volume to substantially 125% weight per volume, an emulsifying agent and one or more osmotic agent means for maintaining the osmolarity of the emulsion comprising an effective amount of a hexahydric alcohol, a sugar, sodium chloride, sodium bicarbonate, potassium phosphate, calcium chloride, magnesium chloride, magnesium sulphate, imidazole, tris(hydroxymethyl)-aminomethane, monobasic sodium phosphate or dibasic sodium phosphate or a biocompatible, non-calcium precipitating combination thereof; with the proviso that when the fluorocarbon is a brominated perfluorocarbon the osmotic agent means does not consist of a combination of sodium phosphates and glycerol.

3. A fluorocarbon emulsion according to claim 1 or claim 2 wherein the osmotic agent means included a hexahydric alcohol.

4. A fluorocarbon emulsion as claimed in claim 1,2 or 3 wherein the emulsifying agent comprises a phospholipid, such as lecithin, and/or an anionic surfactant.

5. A fluorocarbon emulsion as claimed in any one of claims 1-4, wherein the fluorocarbon is selected from a mono-brominated perfluorocarbon, such as 1-bromoseptadeca-fluoroctane, 1-bromotridecafluorohexane or 1-bromo-pentadecafluoroseptane, C4F9CH-CHC4F9 and F-decalin.

6. A fluorocarbon emulsion as claimed in any one of claims 1 to 5, wherein the emulsifying agent comprises a biocompatible fluorinated surfactant.

7. A fluorocarbon emulsion as claimed in claim 6 wherein the fluorinated cosurfactant comprises a fluorinated polyhydroxylated surfactant.

8. A fluorocarbon emulsion as claimed in any one of claims 1 to 7 further comprising a buffering agent comprising imidazole and/or tris(hydroxymethyl)aminomethane.

9. A fluorocarbon emulsion as claimed in Claim 8 wherein the buffering agent group further comprises sodium bicarbonate, monobasic sodium phosphate, dibasic sodium phosphate, magnesium sulphate, magnesium chloride, sodium chloride, potassium chloride, monobasic potassium phosphate or dibasic potassium phosphate or a non-calcium precipitating combination thereof.

10. A fluorocarbon emulsion as claimed in any one of claims 1 to 9, wherein the pH of the emulsion is maintained at from 4.0 to 8.4, preferably from 7.0 to 7.8.

11. A fluorocarbon emulsion as claimed in claim 8 wherein said buffering agent is imidazole and the osmolarity of the emulsion is maintained at from 240 milliosmols to 650 milliosmols.

12. A fluorocarbon emulsion as claimed in any one of claims 2 to 11, wherein the hexahydric alcohol osmotic agent comprises mannitol.

13. A fluorocarbon emulsion as claimed in claim 11 suitable for application to tissue of animal bodies and/or organs thereof wherein the mannitol added to the emulsion is in the range of from 0.25 grams to 1.5 grams of mannitol per 100 millilitres of emulsion.

14. A fluorocarbon emulsion as claimed in any one of claims 1 to 13, which comprises an anti-oxidant.

15. A fluorocarbon emulsion as claimed in claim 14, wherein the anti-oxidant comprises mannitol, a tocopherol such as alpha-tocopherol acetate, ascorbyl palmitate and/or imidazole.

16. A fluorocarbon emulsion as claimed in claim 14 or 15, wherein the antioxidant comprises ascorbic acid, a salt or complex thereof or a non-calcium precipitating combination thereof.

17. A fluorocarbon emulsion as claimed in any one of claims 1 to 16, wherein the fluorocarbon in emulsion is in an amount of from 80% weight per volume to 125% weight per volume.

18. A fluorocarbon emulsion as claimed in any one of the claims 1 to 17, wherein the means for maintaining the osmolarity comprises mannitol, and the osmolarity of the emulsion is maintained at from 240 milliosmols to 650 milliosmols.

19. A fluorocarbon emulsion as claimed in claim 2, wherein the osmotic agent means includes at least a sugar.

20. A fluorocarbon emulsion as claimed in claim 19, wherein the sugar comprises glucose, mannose and/or fructose.

21. A fluorocarbon emulsion as claimed in claim 2, 19 or 20, wherein said osmotic agent means further includes mannitol and said sugar in an effective amount to reduce injury to red blood cells in vitro.

22. A fluorocarbon emulsion for application to animal bodies and organs thereof, comprising a continuous aqueous phase, 50% to 125% weight per volume of a fluorocarbon and an emulsifying agent and osmotic agent means for maintaining the osmolarity of the emulsion in the animal body and organs thereof, wherein the osmotic agent means is characterised by any of the following:
(a) non-glycerol and non-saline;
(b) non-calcium precipitating and suitable for maintaining the pH of the emulsion;
(c) non-saline, non-phosphate and non-glycerol and suitable for maintaining the pH of the emulsion.

23. A method for preparing a fluorocarbon emulsion substantially stable after sterilization and having from 50% weight per volume to 125% weight per volume of fluorocarbon in emulsion, comprising the steps of:
(a) preparing an aqueous phase vehicle by mixing in a sufficient quantity of water, an emulsifying agent, an effective amount of an osmotic agent;
(b) mixing into the vehicle at a measured rate a fluorocarbon to form a mixture;
(c) flowing the said resulting mixture into at least two flow paths;
(d) impinging the said flow paths of the mixture into each other in a cavity under greater than atmospheric pressure;
with the proviso that when the fluorocarbon is a brominated fluorocarbon the osmotic agent means does not consist of a combination of sodium phosphates and glycerol.

24. A method as claimed in claim 23, wherein the vehicle further comprises a buffering agent comprising imidazole and/or tris(hydroxymethyl)aminomethane.

25. A method as claimed in claim 23 or 24, wherein the emulsifying agent comprises lecithin, a fluorinated surfactant or an anionic surfactant.

26. A method as claimed in claim 23,24 or 25, wherein the mixture is made to flow at 1500 feet per second (460 m/s) in the flowing step (c).

27. A method as claimed in any one of claims 23 to 26 wherein the cavity is maintained at approximately 4000 pounds per square inch (28 MN/m^2), and/or the cavity has heat removed, for example by subjecting the cavity to an ice bath, preferably maintained at 5 °C, in the impinging step (d).

28. A method as claimed in any one of claims 23 to 27 wherein the flowing step and the impinging step are repeated, for example four times.

29. A method as claimed in claim 28, further including the steps of collecting the mixture after said impinging step, and sterilizing said mixture by autoclave.

30. A method as claimed in any one of claims 23 to 29, wherein in the vehicle, the osmotic agent, which is preferably non-calcium precipitating, includes a hexahydric alcohol, such as mannitol.

31. A method as claimed in any one of claims 23 to 30 wherein the fluorocarbon is selected from a monobrominated perfluorocarbon (such as 1-bromoseptadecafluoroctane, 1-bromopentadecafluoroseptane or 1-bromotridecafluoro-hexane), C4F9CH-CHC4F9, i-C3F7CH-CHC6F13, C6F13CH = CHC6F13, F-adamantane, F-1, 3-dimethyladamantane, F-decalin, F-4-methyloctahydroquinolidizine, F-4-methyldecahydroquinoline, F-4-cyclohexyl-pyrrolidine, F-2-butyltetrahydrofuran, (CF3)2CFO(CF2CF2)20CF(CF3)2, (CF3)2CFO(CF2CF2)30CF(CF3)2, (CF3)2CFO(CF2CF2)2F, (CF3)2CFO(CF2CF2)3F, (C6F13)20,F[CF(CF3)CF20]2CHFCF3 and a stable, compatible combination thereof.

32. The use of a fluorocarbon emulsion having a continuous phase, a discontinuous phase and a minor amount of an emulsifying agent forming a membrane between the two phases in the preparation of a delivery system for delivering a therapeutic drug into an animal body or an organ thereof.

33. The use as claimed in claim 32, wherein the drug is soluble in the fluorocarbon discontinuous phase or complexed with the membrane formed by the emulsifying agent.

34. The use as claimed in claim 32 or 33 emulsifying agent is lecithin and said drug is lipophilic.

35. The use as claimed in claim 32,33 or 34, wherein the drug is an enzyme, such as streptokinase, an antibiotic, such as cefoxitin, gentamycin, clindamycin and rifampin, a hematopoietic protector, such as imidazole or a derivative thereof, an anti-oxidant, such as mannitol, tocopherols or ascorbyl palmitate, or a thrombolytic enzyme.

Claims for the following Contracting State : ES

1. A process for the preparation of a fluorocarbon emulsion which is substantially stable after heat sterilization, the process comprising admixing a continuous aqueous phase component, a discontinuous phase component comprising a perfluorocarbon (other than a brominated perfluorocarbon) in emulsion in an amount of from 50% W/V to 125% W/V, an emulsifying agent and osmotic agent means, but not a combination of a phospholipid and a glyceride of fatty acids.

2. A process for the preparation of a biocompatible fluorocarbon emulsion for application to animal bodies and organs thereof, the process comprising admixing a continuous aqueous phase, a discontinuous phase comprising a fluorocarbon in emulsion in an amount of from 50% weight per volume to 125% weight per volume, an emulsifying agent and one or more osmotic agent means for maintaining the osmolarity of the emulsion comprising an effective amount of a hexahydric alcohol, a sugar, sodium chloride, sodium bicarbonate, potassium phosphate, calcium chloride, magnesium chloride, magnesium sulphate, imidazole, tris(hydroxymethyl)aminomethane, monobasic sodium phosphate or dibasic sodium phosphate or a biocompatible, non-calcium precipitating combination thereof, the emulsion not comprising a combination of phospholipid and glyceride of fatty acids; with the proviso that when the

fluorocarbon is a brominated perfluorocarbon the osmotic agent means does not consist of a combination of sodium phosphates and glycerol.

3. A process according to claim 1 or claim 2 wherein the osmotic agent means included a hexahydric alcohol.

4. A process as claimed in claim 1,2 or 3 wherein the emulsifying agent comprises a phospholipid, such as lecithin, and/or an anionic surfactant.

5. A process as claimed in any one of claims 1-4, wherein the fluorocarbon is selected from a monobrominated perfluorocarbon, such as 1-bromoseptadecafluoroctane, 1-bromotridecafluorohexane or 1-bromopentadecafluoroseptane, C4F9CH-CHC4F9 and F-decalin.

6. A process as claimed in any one of claims 1 to 5, wherein the emulsifying agent comprises a biocompatible fluorinated surfactant.

7. A process as claimed in claim 6 wherein the fluorinated cosurfactant comprises a fluorinated polyhydroxylated surfactant.

8. A process as claimed in any one of claims 1 to 7 further comprising a buffering agent comprising imidazole and/or tris(hydroxymethyl)-aminomethane.

9. A process as claimed in Claim 8 wherein the buffering agent group further comprises sodium bicarbonate, monobasic sodium phosphate, dibasic sodium phosphate, magnesium sulphate, magnesium chloride, sodium chloride, potassium chloride, monobasic potassium phosphate or dibasic potassium phosphate or a non-calcium precipitating combination thereof.

10. A process as claimed in any one of claims 1 to 9, wherein the pH of the emulsion is maintained at from 4.0 to 8.4, preferably from 7.0 to 7.8.

11. A process as claimed in claim 8 wherein said buffering agent is imidazole and the osmolarity of the emulsion is maintained at from 240 milliosmols to 650 milliosmols.

12. A process as claimed in any one of claims 2 to 11, wherein the hexahydric alcohol osmotic agent comprises mannitol.

13. A process as claimed in claim 11 suitable for application to tissue of animal bodies and/or organs thereof wherein the mannitol added to the emulsion is in the range of from 0.25 grams to 1.5 grams of mannitol per 100 millilitres of emulsion.

14. A process as claimed in any one of claims 1 to 13, which comprises an anti-oxidant.

15. A process as claimed in claim 14, wherein the anti-oxidant comprises mannitol, a tocopherol such as alpha-tocopherol acetate, ascorbyl palmitate and/or imidazole.

16. A fluorocarbon emulsion as claimed in claim 14 or 15, wherein the antioxidant comprises ascorbic acid, a salt or complex thereof or a non-calcium precipitating combination thereof.

17. A fluorocarbon emulsion as claimed in any one of claims 1 to 16, wherein the fluorocarbon in emulsion is in an amount of from 80% weight per volume to 125% weight per volume.

18. A process as claimed in any one of the claims 1 to 17, wherein the means for maintaining the osmolarity comprises mannitol, and the osmolarity of the emulsion is maintained at from 240 milliosmols to 650 milliosmols.

19. A process as claimed in claim 2, wherein the osmotic agent means includes at least a sugar.

20. A process as claimed in claim 19, wherein the sugar comprises glucose, mannose and/or fructose.

21. A process as claimed in claim 2, 19 or 20, wherein said osmotic agent means further includes mannitol and said sugar in an effective amount to reduce injury to red blood cells in vitro.

22. A fluorocarbon emulsion for application to animal bodies and organs thereof, comprising a continuous aqueous phase, 50% to 125% weight per volume of a fluorocarbon and an emulsifying agent and osmotic agent means for maintaining the osmolarity of the emulsion in the animal body and organs thereof but not a combination of phospholipid and glyceride of fatty acids, wherein the osmotic agent means is characterised by any of the following:
(a) non-glycerol and non-saline;
(b) non-calcium precipitating and suitable for maintaining the pH of the emulsion;
(c) non-saline, non-phosphate and non-glycerol and suitable for maintaining the pH of the emulsion.

23. A method for preparing a fluorocarbon emulsion substantially stable after sterilization and having from 50% weight per volume to 125% weight per volume of fluorocarbon in emulsion, comprising the steps of:
(a) preparing an aqueous phase vehicle by mixing in a sufficient quantity of water, an emulsifying agent, an effective amount of an osmotic agent;
(b) mixing into the vehicle at a measured rate a fluorocarbon to form a mixture;
(c) flowing the said resulting mixture into at least two flow paths;
(d) impinging the said flow paths of the mixture into each other in a cavity under greater than atmospheric pressure;
the emulsion not comprising a combination of phospholipid and glyceride of fatty acids, and with the proviso that when the fluorocarbon is a brominated fluorocarbon the osmotic agent means does not consist of a combination of sodium phosphates and glycerol.

24. A method as claimed in claim 23, wherein the vehicle further comprises a buffering agent comprising imidazole and/or tris(hydroxymethyl)aminomethane.

25. A method as claimed in claim 23 or 24, wherein the emulsifying agent comprises lecithin, a fluorinated surfactant or an anionic surfactant.

26. A method as claimed in claim 23,24 or 25, wherein the mixture is made to flow at 1500 feet per second (460 m/s) in the flowing step (c).

27. A method as claimed in any one of claims 23 to 26 wherein the cavity is maintained at 4000 pounds per square inch (28 MN/m^2), and/or the cavity has heat removed, for example by subjecting the cavity to an ice bath, preferably maintained at 5 °C, in the impinging step (d).

28. A method as claimed in any one of claims 23 to 27 wherein the flowing step and the impinging step are repeated, for example four times.

29. A method as claimed in claim 28, further including the steps of collecting the mixture after said impinging step, and sterilizing said mixture by autoclave.

30. A method as claimed in any one of claims 23 to 29, wherein in the vehicle, the osmotic agent, which is preferably non-calcium precipitating, includes a hexahydric alcohol, such as mannitol.

31. A method as claimed in any one of claims 23 to 30 wherein the fluorocarbon is selected from a mono-brominated perfluorocarbon (such as 1-bromoseptadecafluoroctane, 1-bromopentadecafluoroseptane or 1-bromotridecafluoro-hexane), C4F9CH-CHC4F9, i-C3F7CH-CHC6F13, C6F13CH = CHC6F13, F-adamantane, F-1, 3-dimethyladamantane, F-decalin, F-4-methyloctahydroquinolidizine, F-4-methyldecahydroquinoline, F-4-cyclohexyl-pyrrolidine, F-2-butyltetrahydrofuran, (CF3)2CFO(CF2CF2)20CF(CF3)2, (CF3)2CFO(CF2CF2)30CF(CF3)2, (CF3)2CFO(CF2CF2)2F, (CF3)2CFO(CF2CF2)3F, (C6F13)20,F[CF(CF3)CF20]2CHFCF3 and a stable, compatible combination thereof.

32. The use of a fluorocarbon emulsion having a continuous phase, a discontinuous phase and a minor amount of an emulsifying agent forming a membrane between the two phases in the preparation of a delivery system for delivering a therapeutic drug into an animal body or an organ thereof.

33. The use as claimed in claim 32, wherein the drug is soluble in the fluorocarbon discontinuous phase or complexed with the membrane formed by the emulsifying agent.

34. The use as claimed in claim 32 or 33 emulsifying agent is lecithin and said drug is lipophilic.

35. The use as claimed in claim 32,33 or 34, wherein the drug is an enzyme, such as streptokinase, an antibiotic, such as cefoxitin, gentamycin, clindamycin and rifampin, a hematopoietic protector, such as imidazole or a derivative thereof, an anti-oxidant, such as mannitol, tocopherols or ascorbyl palmitate, or a thrombolytic enzyme.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : BE, DE, FR, GB, IT, LU, NL, SE

1. Fluorkohlenwasserstoffemulsion, die nach Wärmesterilisation stabil ist und eine kontinuierliche wässerige Phase, eine einen Perfluorkohlenwasserstoff (mit Ausnahme eines bromierten Perfluorkohlenwasserstoffs) in Emulsion in einer Menge von 50% (Gew./Vol.) bis 125% (Gew./Vol.) enthaltende diskontinuierliche Phase, einen Emulgator und einen Osmosewirkstoff, aber keine Kombination aus einem Phospholipid und einem Glycerid von Fettsäuren aufweist.

2. Biokompatible Fluorkohlenwasserstoffemulsion zur Anwendung an Tierkörpern und Organen davon, umfassend eine kontinuierliche wässerige Phase, eine einen Fluorkohlenwasserstoff in Emulsion in einer Menge von 50% (Gew./Vol.) bis 125% (Gew./Vol.) enthaltende diskontinuierliche Phase, einen Emulgator und einen oder mehrere Osmosewirkstoffe, um die Osmolarität der Emulsion beizubehalten, der eine wirksame Menge eines sechswertigen Alkohols, eines Zuckers, Natriumchlorid, Natriumbikarbonat, Kaliumphosphat, Kalziumchlorid, Magnesiumchlorid, Magnesiumsulfat, eines Imidazols, tris-(Hydroxymethyl)aminomethan, einbasisches Natriumphosphat oder zweibasisches Natriumphosphat oder eine biokompatible nicht-kalziumausfällende Kombination davon enthält/enthalten, wobei die Emulsion keine Kombination aus Phospholipid und Glycerid von Fettsäuren enthält; mit der Maßgabe, daß, wenn der Fluorkohlenwasserstoff ein bromierter Perfluorkohlenwasserstoff ist, der Osmosewirkstoff nicht aus einer Kombination aus Natriumphosphaten und Glycerin besteht.

3. Fluorkohlenwasserstoffemulsion nach Anspruch 1 oder 2, worin der Osmosewirkstoff einen sechswertigen Alkohol enthält.

4. Fluorkohlenwasserstoffemulsion nach Anspruch 1, 2 oder 3, worin der Emulgator ein Phospholipid wie z.B. Lecithin und/oder ein anionisches oberflächenaktives Mittel enthält.

5. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 4, worin der Fluorkohlenwasserstoff aus monobromiertem Perfluorkohlenwasserstoff, wie z.B. 1-Bromheptadecafluoroktan, 1-Bromtridecafluorhexan oder 1-Brompentadecafluorheptan, C4F9CH-CHC4F9 und F-Decalin ausgewählt ist.

6. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 5, worin der Emulgator ein biokompatibles fluoriertes oberflächenaktives Mittel enthält.

7. Fluorkohlenwasserstoffemulsion nach Anspruch 6, worin das fluorierte Co-oberflächenaktive Mittel ein fluoriertes polyhydroxyliertes oberflächenaktives Mittel enthält.

8. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 7, das weiters einen Puffer umfaßt, der Imidazol und/oder tris(Hydroxymethyl)aminomethan enthält.

9. Fluorkohlenwasserstoffemulsion nach Anspruch 8, worin die Puffergruppe weiters Natriumbikarbonat, einbasisches Natriumphosphat, zweibasisches Natriumphosphat, Magnesiumsulfat, Magnesiumchlorid, Natriumchlorid, Kaliumchlorid, einbasisches Kaliumphosphat oder zweibasisches Kaliumphosphat oder eine nicht-kalziumausfällende Kombination daraus umfaßt.

10. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 9, worin der pH-Wert der Emulsion bei 4,0 bis 8,4, vorzugsweise 7,0 bis 7,8, gehalten wird.

11. Fluorkohlenwasserstoffemulsion nach Anspruch 8, worin der genannte Puffer Imidazol ist und die Osmolarität der Emulsion bei 240 Milliosmol bis 650 Milliosmol gehalten wird.

12. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 2 bis 11, worin der Osmosewirkstoff aus sechswertigem Alkohol Mannit umfaßt.

13. Fluorkohlenwasserstoffemulsion nach Anspruch 11, die zur Anwendung an Gewebe von Tierkörpern und/oder Organen davon geeignet ist, worin der der Emulsion zugegebene Mannit im Bereich von 0,25 g bis 1,5 g Mannit pro 100 ml Emulsion liegt.

14. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 13, die einen Oxidationshemmer umfaßt.

15. Fluorkohlenwasserstoffemulsion nach Anspruch 14, worin der Oxidationshemmer Mannit, ein Tocopherol wie z.B. alpha-Tocopherolacetat, Ascorbylpalmitat und/oder Imidazol umfaßt.

16. Fluorkohlenwasserstoffemulsion nach Anspruch 14 oder 15, worin der Oxidationshemmer Ascorbinsäure, ein Salz oder einen Komplex davon oder eine nicht-kalziumausfällende Kombination daraus umfaßt.

17. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 16, worin der Fluorkohlenwasserstoff in Emulsion in einer Menge von 80 % (Gew./Vol.) bis 125 % (Gew./Vol.) vorliegt.

18. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 17, worin das Mittel zur Beibehaltung der Osmolarität Mannit umfaßt und die Osmolarität der Emulsion bei 240 Milliosmol bis 650 Milliosmol gehalten wird.

19. Fluorkohlenwasserstoffemulsion nach Anspruch 2, worin der Osmosewirkstoff zumindest einen Zucker enthält.

20. Fluorkohlenwasserstoffemulsion nach Anspruch 19, worin der Zucker Glukose, Mannose und/oder Fruktose umfaßt.

21. Fluorkohlenwasserstoffemulsion nach Anspruch 2, 19 oder 20, worin der genannte Osmosewirkstoff weiters Mannit und den genannten Zucker in einer wirksamen Menge umfaßt, um die Schädigung roter Blutkörperchen in vitro zu verringern.

22. Fluorkohlenwasserstoffemulsion zur Anwendung an Tierkörpern und Organen davon, umfassend eine kontinuierliche wässerige Phase, 50 % (Gew./Vol.) bis 125 % (Gew./Vol.) eines Fluorkohlenwasserstoffs und einen Emulgator und einen Osmosewirkstoff, um die Osmolarität der Emulsion im Tierkörper und Organen davon beizubehalten, aber nicht eine Kombination aus Phospholipid und Glycerid von Fettsäuren, worin der Osmosewirkstoff durch irgendeines der folgenden gekennzeichnet ist:
    (a) nicht Glycerin und nicht auf Salzbasis;
    (b) nicht-Kalziumausfällend und geeignet, um den pH-Wert der Emulsion beizubehalten;
    (c) nicht auf Salzbasis, nicht Phosphat und nicht Glycerin und geeignet, um den pH-Wert der Emulsion beizubehalten.

23. Verfahren zur Herstellung einer Fluorkohlenwasserstoffemulsion, die nach Sterilisation im wesentlichen stabil ist und von 50 % (Gew./Vol.) bis 125 % (Gew./Vol.) Fluorkohlenwasserstoff in Emulsion aufweist, folgende Schritte umfassend:
    (a) das Herstellen eines Wasserphasenvehikels durch Mischen einer ausreichenden Menge von Wasser, eines Emulgators, einer wirksamen Menge eines Osmosewirkstoffs;
    (b) das Einmischen eines Fluorkohlenwasserstoffs mit einer gemessenen Rate in das Vehikel, um eine Mischung zu bilden;
    (c) das Fließenlassen der genannten resultierenden Mischung in zumindest zwei Strömungswegen;
    (d) das Auftreffenlassen der genannten Strömungswege der Mischung aufeinander in einem Hohlraum unter einem überatmosphärischen Druck;
wobei die Emulsion keine Kombination aus Phospholipid und Glycerid von Fettsäuren umfaßt, und mit der Maßgabe, daß, wenn der Fluorkohlenwasserstoff ein bromierter Fluorkohlenwasserstoff ist, der

Osmosewirkstoff nicht aus einer Kombination aus Natriumphosphaten und Glycerin besteht.

24. Verfahren nach Anspruch 23, worin das Vehikel weiters einen Puffer umfaßt, der Imidazol und/oder tris-(Hydroxymethyl)aminomethan umfaßt.

25. Verfahren nach Anspruch 23 oder 24, worin der Emulgator Lecithin, ein fluoriertes oberflächenaktives Mittel oder ein anionisches oberflächenaktives Mittel umfaßt.

26. Verfahren nach Anspruch 23, 24 oder 25, worin die Mischung im Fließschritt (c) mit 1500 Fuß pro Sekunde (460 m/s) zum Fließen gebracht wird.

27. Verfahren nach einem der Ansprüche 23 bis 26, worin der Hohlraum beim Auftreffschritt (d) bei 4000 Pfund pro Quadratinch (28 MN/m^2) gehalten wird und/oder dem Hohlraum Wärme entzogen wird, beispielsweise indem der Hohlraum einem vorzugsweise bei 5 °C gehaltenen Eisbad ausgesetzt wird.

28. Verfahren nach einem der Ansprüche 23 bis 27, worin der Fließschritt und der Auftreffschritt, beispielsweise viermal, wiederholt werden.

29. Verfahren nach Anspruch 28, das weiters die Schritte des Sammelns der Mischung nach dem genannten Auftreffschritt und des Sterilisierens der genannten Mischung durch Autoklavieren umfaßt.

30. Verfahren nach einem der Ansprüche 23 bis 29, worin der Osmosewirkstoff im Vehikel, der vorzugsweise nicht-kalziumausfällend ist, einen sechswertigen Alkohol wie z.B. Mannit enthält.

31. Verfahren nach einem der Ansprüche 23 bis 30, worin der Fluorkohlenwasserstoff aus einem monobromierten Perfluorkohlenwasserstoff (wie z.B. 1-Bromheptadecafluoroktan, 1-Brompentadecafluorheptan oder 1-Bromtridecafluorhexan), C4F9CH-CHC4F9, i-C3F7CH-CHC6F13, C6F13CH = CHC6F13, F-Adamantan, F-1,3-Dimethyladamantan, F-Decalin, F-4-Methyloctahydrochinolidizin, F-4-Methyldecahydrochinolin, F-4-Zyklohexylpyrrolidin, F-2-Butyltetrahydrofuran, (CF3)2CFO(CF2CF2)20CF(CF3)2, (CF3)-2CFO(CF2CF2)30CF(CF3)2, (CF3)2CFO(CF2CF2)2F, (CF3)2CFO(CF2CF2)3F, (C6F13)20, F[CF(CF3)-CF20]2CHFCF3 und einer stabilen kompatiblen Kombination daraus ausgewählt ist.

32. Verwendung einer Fluorkohlenwasserstoffemulsion mit einer kontinuierlichen Phase, einer diskontinuierlichen Phase und einer geringen Menge eines Emulgators, der eine Membran zwischen den beiden Phasen bildet, bei der Herstellung eines Abgabesystems zur Abgabe eines therapeutischen Arzneimittels in einen Tierkörper oder ein Organ davon.

33. Verwendung nach Anspruch 32, worin das Arzneimittel in der diskontinuierlichen Fluorkohlenwasserstoffphase löslich oder mit der Membran komplexiert ist, die durch den Emulgator gebildet wird.

34. Verwendung nach Anspruch 32 oder 33, wobei der Emulgator Lecithin ist und das genannte Arzneimittel lipophil ist.

35. Verwendung nach Anspruch 32,33 oder 34, worin das Arzneimittel ein Enzym, wie z.B. Streptokinase, ein Antibiotikum wie Cefoxitin, Gentamycin, Clindamycin und Rifampin, ein hämatopoietischer Protektor wie z.B. Imidazol oder ein Derivat davon, ein Oxidationshemmer wie z.B. Mannit, Tocopherole oder Ascorbylpalmitat, oder ein thrombolytisches Enzym ist.

Patentansprüche für folgenden Vertragsstaat : AT

1. Fluorkohlenwasserstoffemulsion, die nach Wärmesterilisation stabil ist und eine kontinuierliche wässerige Phase, eine einen Perfluorkohlenwasserstoff (mit Ausnahme eines bromierten Perfluorkohlenwasserstoffs) in Emulsion in einer Menge von 50% (Gew./Vol.) bis 125% (Gew./Vol.) enthaltende diskontinuierliche Phase, einen Emulgator und einen Osmosewirkstoff aufweist.

2. Biokompatible Fluorkohlenwasserstoffemulsion zur Anwendung an Tierkörpern und Organen davon, umfassend eine kontinuierliche wässerige Phase, eine einen Fluorkohlenwasserstoff in Emulsion in einer Menge von 50% (Gew./Vol.) bis im wesentlichen 125% (Gew./Vol.) enthaltende diskontinuierliche

Phase, einen Emulgator und einen oder mehrere Osmosewirkstoffe, um die Osmolarität der Emulsion beizubehalten, der eine wirksame Menge eines sechswertigen Alkohols, eines Zuckers, Natriumchlorid, Natriumbikarbonat, Kaliumphosphat, Kalziumchlorid, Magnesiumchlorid, Magnesiumsulfat, eines Imidazols, tris(Hydroxymethyl)aminomethan, einbasisches Natriumphosphat oder zweibasisches Natriumphosphat oder eine biokompatible nicht-kalziumausfällende Kombination davon enthält/enthalten; mit der Maßgabe, daß, wenn der Fluorkohlenwasserstoff ein bromierter Perfluorkohlenwasserstoff ist, der Osmosewirkstoff nicht aus einer Kombination aus Natriumphosphaten und Glycerin besteht.

3. Fluorkohlenwasserstoffemulsion nach Anspruch 1 oder 2, worin der Osmosewirkstoff einen sechswertigen Alkohol enthält.

4. Fluorkohlenwasserstoffemulsion nach Anspruch 1, 2 oder 3, worin der Emulgator ein Phospholipid wie z.B. Lecithin und/oder ein anionisches oberflächenaktives Mittel enthält.

5. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 4, worin der Fluorkohlenwasserstoff aus monobromiertem Perfluorkohlenwasserstoff, wie z.B. 1-Bromheptadecafluoroktan, 1-Bromtridecafluorhexan oder 1-Brompentadecafluorheptan, C4F9CH-CHC4F9 und F-Decalin ausgewählt ist.

6. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 5, worin der Emulgator ein biokompatibles fluoriertes oberflächenaktives Mittel enthält.

7. Fluorkohlenwasserstoffemulsion nach Anspruch 6, worin das fluorierte co-oberflächenaktive Mittel ein fluoriertes polyhydroxyliertes oberflächenaktives Mittel enthält.

8. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 7, das weiters einen Puffer umfaßt, der Imidazol und/oder tris(Hydroxymethyl)aminomethan enthält.

9. Fluorkohlenwasserstoffemulsion nach Anspruch 8, worin die Puffergruppe weiters Natriumbikarbonat, einbasisches Natriumphosphat, zweibasisches Natriumphosphat, Magnesiumsulfat, Magnesiumchlorid, Natriumchlorid, Kaliumchlorid, einbasisches Kaliumphosphat oder zweibasisches Kaliumphosphat oder eine nicht-kalziumausfällende Kombination daraus umfaßt.

10. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 9, worin der pH-Wert der Emulsion bei 4,0 bis 8,4, vorzugsweise 7,0 bis 7,8, gehalten wird.

11. Fluorkohlenwasserstoffemulsion nach Anspruch 8, worin der genannte Puffer Imidazol ist und die Osmolarität der Emulsion bei von 240 Milliosmol bis 650 Milliosmol gehalten wird.

12. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 2 bis 11, worin der Osmosewirkstoff aus sechswertigem Alkohol Mannit umfaßt.

13. Fluorkohlenwasserstoffemulsion nach Anspruch 11, die zur Anwendung an Gewebe von Tierkörpern und/oder Organen davon geeignet ist, worin der der Emulsion zugegebene Mannit im Bereich von 0,25 g bis 1,5 g Mannit pro 100 ml Emulsion liegt.

14. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 13, die einen Oxidationshemmer umfaßt.

15. Fluorkohlenwasserstoffemulsion nach Anspruch 14, worin der Oxidationshemmer Mannit, ein Tocopherol wie z.B. alpha-Tocopherolacetat, Ascorbylpalmitat und/oder Imidazol umfaßt.

16. Fluorkohlenwasserstoffemulsion nach Anspruch 14 oder 15, worin der Oxidationshemmer Ascorbinsäure, ein Salz oder einen Komplex davon oder eine nicht-kalziumausfällende Kombination daraus umfaßt.

17. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 16, worin der Fluorkohlenwasserstoff in Emulsion in einer Menge von 80 % (Gew./Vol.) bis 125 % (Gew./Vol.) vorliegt.

18. Fluorkohlenwasserstoffemulsion nach einem der Ansprüche 1 bis 17, worin das Mittel zur Beibehaltung der Osmolarität Mannit umfaßt und die Osmolarität der Emulsion bei 240 Milliosmol bis 650 Milliosmol gehalten wird.

19. Fluorkohlenwasserstoffemulsion nach Anspruch 2, worin der Osmosewirkstoff zumindest einen Zucker enthält.

20. Fluorkohlenwasserstoffemulsion nach Anspruch 19, worin der Zucker Glukose, Mannose und/oder Fruktose umfaßt.

21. Fluorkohlenwasserstoffemulsion nach Anspruch 2, 19 oder 20, worin der genannte Osmosewirkstoff weiters Mannit und den genannten Zucker in einer wirksamen Menge umfaßt, um die Schädigung roter Blutkörperchen in vitro zu verringern.

22. Fluorkohlenwasserstoffemulsion zur Anwendung an Tierkörpern und Organen davon, umfassend eine kontinuierliche wässerige Phase, 50 % (Gew./Vol.) bis 125 % (Gew./Vol.) eines Fluorkohlenwasserstoffs und einen Emulgator und einen Osmosewirkstoff, um die Osmolarität der Emulsion im Tierkörper und Organen davon beizubehalten, worin der Osmosewirkstoff durch irgendeines der folgenden gekennzeichnet ist:
(a) nicht Glycerin und nicht auf Salzbasis;
(b) nicht-Kalziumausfällend und geeignet, um den pH-Wert der Emulsion beizubehalten;
(c) nicht auf Salzbasis, nicht Phosphat und nicht Glycerin und geeignet, um den pH-Wert der Emulsion beizubehalten.

23. Verfahren zur Herstellung einer Fluorkohlenwasserstoffemulsion, die nach Sterilisation im wesentlichen stabil ist und von 50 % (Gew./Vol.) bis 125 % (Gew./Vol.) Fluorkohlenwasserstoff in Emulsion aufweist, folgende Schritte umfassend:
(a) das Herstellen eines Wasserphasenvehikels durch Mischen einer ausreichendem Menge von Wasser, eines Emulgators, einer wirksamen Menge eines Osmosewirkstoffs;
(b) das Einmischen eines Fluorkohlenwasserstoffs mit einer gemessenen Rate in das Vehikel, um eine Mischung zu bilden;
(c) das Fließenlassen der genannten resultierenden Mischung in zumindest zwei Strömungswegen;
(d) das Auftreffenlassen der genannten Strömungswege der Mischung aufeinander in einem Hohlraum unter überatmosphärischem Druck;
mit der Maßgabe, daß, wenn der Fluorkohlenwasserstoff ein bromierter Fluorkohlenwasserstoff ist, der Osmosewirkstoff nicht aus einer Kombination aus Natriumphosphaten und Glycerin besteht.

24. Verfahren nach Anspruch 23, worin das Vehikel weiters einen Puffer umfaßt, der Imidazol und/oder tris-(Hydroxymethyl)aminomethan umfaßt.

25. Verfahren nach Anspruch 23 oder 24, worin der Emulgator Lecithin, ein fluoriertes oberflächenaktives Mittel oder ein anionisches oberflächenaktives Mittel umfaßt.

26. Verfahren nach Anspruch 23, 24 oder 25, worin die Mischung im Fließschritt (c) mit 1500 Fuß pro Sekunde (460 m/s) zum Fließen gebracht wird.

27. Verfahren nach einem der Ansprüche 23 bis 26, worin der Hohlraum beim Auftreffschritt (d) bei etwa 4000 Pfund pro Quadratinch (28 MN/m^2) gehalten wird und/oder dem Hohlraum Wärme entzogen wird, beispielsweise indem der Hohlraum einem vorzugsweise bei 5 °C gehaltenen Eisbad ausgesetzt wird.

28. Verfahren nach einem der Ansprüche 23 bis 27, worin der Fließschritt und der Auftreffschritt, beispielsweise viermal, wiederholt werden.

29. Verfahren nach Anspruch 28, das weiters die Schritte des Sammelns der Mischung nach dem genannten Auftreffschritt und des Sterilisierens der genannten Mischung durch Autoklavieren umfaßt.

30. Verfahren nach einem der Ansprüche 23 bis 29, worin der Osmosewirkstoff im Vehikel, der vorzugsweise nicht-kalziumausfällend ist, einen sechswertigen Alkohol wie z.B. Mannit enthält.

31. Verfahren nach einem der Ansprüche 23 bis 30, worin der Fluorkohlenwasserstoff aus einem monobromierten Perfluorkohlenwasserstoff (wie z.B. 1-Bromheptadecafluoroktan, 1-Brompentadecafluorheptan oder 1-Bromtridecafluorhexan), C4F9CH-CHC4F9, i-C3F7CH-CHC6F13, C6F13CH = CHC6F13, F-Adamantan, F-1,3-Dimethyladamantan, F-Decalin, F-4-Methyloctahydrochinolidizin, F-4-Methyldecahydrochinolin, F-4-Zyklohexylpyrrolidin, F-2-Butyltetrahydrofuran, (CF3)2CFO(CF2CF2)20CF(CF3)2, (CF3)-2CFO(CF2CF2)30CF(CF3)2, (CF3)2CFO(CF2CF2)2F, (CF3)2CFO(CF2CF2)3F, (C6F13)20, F[CF(CF3)-CF20]2CHFCF3 und einer stabilen kompatiblen Kombination daraus ausgewählt ist.

32. Verwendung einer Fluorkohlenwasserstoffemulsion mit einer kontinuierlichen Phase, einer diskontinuierlichen Phase und einer geringen Menge eines Emulgators, der eine Membran zwischen den beiden Phasen bildet, bei der Herstellung eines Abgabesystems zur Abgabe eines therapeutischen Arzneimittels in einen Tierkörper oder ein Organ davon.

33. Verwendung nach Anspruch 32, worin das Arzneimittel in der diskontinuierlichen Fluorkohlenwasserstoffphase löslich oder mit der Membran komplexiert ist, die durch den Emulgator gebildet wird.

34. Verwendung nach Anspruch 32 oder 33, wobei der Emulgator Lecithin ist und das genannte Arzneimittel lipophil ist.

35. Verwendung nach Anspruch 32,33 oder 34, worin das Arzneimittel ein Enzym wie z.B. Streptokinase, ein Antibiotikum wie z.B. Cefoxitin, Gentamycin, Clindamycin und Rifampin, ein hämatopoietischer Protektor wie z.B. Imidazol oder ein Derivat davon, ein Oxidationshemmer wie z.B. Mannit, Tocopherole oder Ascorbylpalmitat, oder ein thrombolytisches Enzym ist.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Fluorkohlenwasserstoffemulsion, die nach Wärmesterilisation im wesentlichen stabil ist, wobei das Verfahren das Mischen einer kontinuierlichen wässerigen Phasenkomponente, einer einen Perfluorkohlenwasserstoff (mit Ausnahme eines bromierten Perfluorkohlenwasserstoffs) in Emulsion in einer Menge von 50% (Gew./Vol.) bis 125% (Gew./Vol.) enthaltenden diskontinuierlichen Phase, eines Emulgators und eines Osmosewirkstoffs, aber keiner Kombination aus einem Phospholipid und einem Glycerid von Fettsäuren, umfaßt.

2. Verfahren zur Herstellung einer biokompatiblen Fluorkohlenwasserstoffemulsion zur Anwendung an Tierkörpern und Organen davon, wobei das Verfahren das Mischen einer kontinuierlichen wässerigen Phase, einer einen Fluorkohlenwasserstoff in Emulsion in einer Menge von 50% (Gew./Vol.) bis 125% (Gew./Vol.) enthaltenden diskontinuierlichen Phase, eines Emulgators und eines oder mehrerer Osmosewirkstoffe umfaßt, um die Osmolarität der Emulsion beizubehalten, der eine wirksame Menge eines sechswertigen Alkohols, eines Zuckers, Natriumchlorid, Natriumbikarbonat, Kaliumphosphat, Kalziumchlorid, Magnesiumchlorid, Magnesiumsulfat, eines Imidazols, tris(Hydroxymethyl)aminomethan, einbasisches Natriumphosphat oder zweibasisches Natriumphosphat oder eine biokompatible nicht-kalziumausfällende Kombination davon enthält/enthalten, wobei die Emulsion keine Kombination aus Phospholipid und Glycerid von Fettsäuren enthält; mit der Maßgabe, daß, wenn der Fluorkohlenwasserstoff ein bromierter Perfluorkohlenwasserstoff ist, der Osmosewirkstoff nicht aus einer Kombination aus Natriumphosphaten und Glycerin besteht.

3. Verfahren nach Anspruch 1 oder 2, worin der Osmosewirkstoff einen sechswertigen Alkohol enthält.

4. Verfahren nach Anspruch 1, 2 oder 3, worin der Emulgator ein Phospholipid wie z.B. Lecithin und/oder ein anionisches oberflächenaktives Mittel enthält.

5. Verfahren nach einem der Ansprüche 1 bis 4, worin der Fluorkohlenwasserstoff aus monobromiertem Perfluorkohlenwasserstoff, wie z.B. 1-Bromheptadecafluoroktan, 1-Bromtridecafluorhexan oder 1-Brompentadecafluorheptan, C4F9CH-CHC4F9 und F-Decalin ausgewählt ist.

6. Verfahren nach einem der Ansprüche 1 bis 5, worin der Emulgator ein biokompatibles fluoriertes oberflächenaktives Mittel enthält.

7. Verfahren nach Anspruch 6, worin das fluorierte co-oberflächenaktive Mittel ein fluoriertes polyhydroxyliertes oberflächenaktives Mittel enthält.

8. Verfahren nach einem der Ansprüche 1 bis 7, das weiters einen Puffer umfaßt, der Imidazol und/oder tris(Hydroxymethyl)aminomethan enthält.

9. Verfahren nach Anspruch 8, worin die Puffergruppe weiters Natriumbikarbonat, einbasisches Natriumphosphat, zweibasisches Natriumphosphat, Magnesiumsulfat, Magnesiumchlorid, Natriumchlorid, Kaliumchlorid, einbasisches Kaliumphosphat oder zweibasisches Kaliumphosphat oder eine nicht-kalziumausfällende Kombination daraus umfaßt.

10. Verfahren nach einem der Ansprüche 1 bis 9, worin der pH-Wert der Emulsion bei 4,0 bis 8,4, vorzugsweise 7,0 bis 7,8, gehalten wird.

11. Verfahren nach Anspruch 8, worin der genannte Puffer Imidazol ist und die Osmolarität der Emulsion bei 240 Milliosmol bis 650 Milliosmol gehalten wird.

12. Verfahren nach einem der Ansprüche 2 bis 11, worin der Osmosewirkstoff aus sechswertigem Alkohol Mannit umfaßt.

13. Verfahren nach Anspruch 11, das zur Anwendung an Gewebe von Tierkörpern und/oder Organen davon geeignet ist, worin der der Emulsion zugegebene Mannit im Bereich von 0,25 g bis 1,5 g Mannit pro 100 ml Emulsion liegt.

14. Verfahren nach einem der Ansprüche 1 bis 13, das einen Oxidationshemmer umfaßt.

15. Verfahren nach Anspruch 14, worin der Oxidationshemmer Mannit, ein Tocopherol wie z.B. alpha-Tocopherolacetat, Ascorbylpalmitat und/oder Imidazol umfaßt.

16. Verfahren nach Anspruch 14 oder 15, worin der Oxidationshemmer Ascorbinsäure, ein Salz oder einen Komplex davon oder eine nicht-kalziumausfällende Kombination daraus umfaßt.

17. Verfahren nach einem der Ansprüche 1 bis 16, worin der Fluorkohlenwasserstoff in Emulsion in einer Menge von 80 % (Gew./Vol.) bis 125 % (Gew./Vol.) vorliegt.

18. Verfahren nach einem der Ansprüche 1 bis 17, worin das Mittel zur Beibehaltung der Osmolarität Mannit umfaßt und die Osmolarität der Emulsion bei 240 Milliosmol bis 650 Milliosmol gehalten wird.

19. Verfahren nach Anspruch 2, worin der Osmosewirkstoff zumindest einen Zucker enthält.

20. Verfahren nach Anspruch 19, worin der Zucker Glukose, Mannose und/oder Fruktose umfaßt.

21. Verfahren nach Anspruch 2, 19 oder 20, worin der genannte Osmosewirkstoff weiters Mannit und den genannten Zucker in einer wirksamen Menge umfaßt, um die Schädigung roter Blutkörperchen in vitro zu verringern.

22. Fluorkohlenwasserstoffemulsion zur Anwendung an Tierkörpern und Organen davon, umfassend eine kontinuierliche wässerige Phase, 50 % (Gew./Vol.) bis 125 % (Gew./Vol.) eines Fluorkohlenwasserstoffs und einen Emulgator und einen Osmosewirkstoff, um die Osmolarität der Emulsion im Tierkörper und Organen davon beizubehalten, aber nicht eine Kombination aus Phospholipid und Glycerid von Fettsäuren, worin der Osmosewirkstoff durch irgendeines der folgenden gekennzeichnet ist:
(a) nicht Glycerin und nicht auf Salzbasis;
(b) nicht-kalziumausfällend und geeignet, um den pH-Wert der Emulsion beizubehalten;
(c) nicht auf Salzbasis, nicht Phosphat und nicht Glycerin und geeignet, um den pH-Wert der Emulsion beizubehalten.

23. Verfahren zur Herstellung einer Fluorkohlenwasserstoffemulsion, die nach Sterilisation im wesentlichen stabil ist und von 50 % (Gew./Vol.) bis 125 % (Gew./Vol.) Fluorkohlenwasserstoff in Emulsion aufweist,

folgende Schritte umfassend:

(a) das Herstellen eines Wasserphasenvehikels durch Mischen einer ausreichenden Menge von Wasser, eines Emulgators, einer wirksamen Menge eines Osmosewirkstoffs;

(b) das Einmischen eines Fluorkohlenwasserstoffs mit einer gemessenen Rate in das Vehikel, um eine Mischung zu bilden;

(c) das Fließenlassen der genannten resultierenden Mischung in zumindest zwei Strömungswegen;

(d) das Auftreffenlassen der genannten Strömungswege der Mischung aufeinander in einem Hohlraum unter überatmosphärischem Druck;

wobei die Emulsion keine Kombination aus Phospholipid und Glycerid von Fettsäuren umfaßt, und mit der Maßgabe, daß, wenn der Fluorkohlenwasserstoff ein bromierter Fluorkohlenwasserstoff ist, der Osmosewirkstoff nicht aus einer Kombination aus Natriumphosphaten und Glycerin besteht.

24. Verfahren nach Anspruch 23, worin das Vehikel weiters einen Puffer umfaßt, der Imidazol und/oder tris-(Hydroxymethyl)aminomethan umfaßt.

25. Verfahren nach Anspruch 23 oder 24, worin der Emulgator Lecithin, ein fluoriertes oberflächenaktives Mittel oder ein anionisches oberflächenaktives Mittel umfaßt.

26. Verfahren nach Anspruch 23, 24 oder 25, worin die Mischung im Fließschritt (c) mit 1500 Fuß pro Sekunde (460 m/s) zum Fließen gebracht wird.

27. Verfahren nach einem der Ansprüche 23 bis 26, worin der Hohlraum beim Auftreffschritt (d) bei 4000 Pfund pro Quadratinch (28 MN/m^2) gehalten wird und/oder dem Hohlraum Wärme entzogen wird, beispielsweise indem der Hohlraum einem vorzugsweise bei 5 °C gehaltenen Eisbad ausgesetzt wird.

28. Verfahren nach einem der Ansprüche 23 bis 27, worin der Fließschritt und der Auftreffschritt, beispielsweise viermal, wiederholt werden.

29. Verfahren nach Anspruch 28, das weiters die Schritte des Sammelns der Mischung nach dem genannten Auftreffschritt und des Sterilisierens der genannten Mischung durch Autoklavieren umfaßt.

30. Verfahren nach einem der Ansprüche 23 bis 29, worin der Osmosewirkstoff im Vehikel, der vorzugsweise nicht-kalziumausfällend ist, einen sechswertigen Alkohol wie z.B. Mannit enthält.

31. Verfahren nach einem der Ansprüche 23 bis 30, worin der Fluorkohlenwasserstoff aus einem monobromierten Perfluorkohlenwasserstoff (wie z.B. 1-Bromheptadecafluoroktan, 1-Brompentadecafluorheptan oder 1-Bromtridecafluorhexan), C4F9CH-CHC4F9, i-C3F7CH-CHC6F13, C6F13CH = CHC6F13, F-Adamantan, F-1,3-Dimethyladamantan, F-Decalin, F-4-Methyloctahydrochinolidizin, F-4-Methyldecahydrochinolin, F-4-Zyklohexylpyrrolidin, F-2-Butyltetrahydrofuran, (CF3)2CFO(CF2CF2)20CF(CF3)2, (CF3)-2CFO(CF2CF2)30CF(CF3)2, (CF3)2CFO(CF2CF2)2F, (CF3)2CFO(CF2CF2)3F, (C6F13)20, F[CF(CF3)-CF20]2CHFCF3 und einer stabilen kompatiblen Kombination daraus ausgewählt ist.

32. Verwendung einer Fluorkohlenwasserstoffemulsion mit einer kontinuierlichen Phase, einer diskontinuierlichen Phase und einer geringen Menge eines Emulgators, der eine Membran zwischen den beiden Phasen bildet, bei der Herstellung eines Abgabesystems zur Abgabe eines therapeutischen Arzneimittels in einen Tierkörper oder ein Organ davon.

33. Verwendung nach Anspruch 32, worin das Arzneimittel in der diskontinuierlichen Fluorkohlenwasserstoffphase löslich oder mit der Membran komplexiert ist, die durch den Emulgator gebildet wird.

34. Verwendung nach Anspruch 32 oder 33, wobei der Emulgator Lecithin ist und das genannte Arzneimittel lipophil ist.

35. Verwendung nach Anspruch 32,33 oder 34, worin das Arzneimittel ein Enzym wie z.B. Streptokinase, ein Antibiotikum wie z.B. Cefoxitin, Gentamycin, Clindamycin und Rifampin, ein hämatopoietischer Protektor wie z.B. Imidazol oder ein Derivat davon, ein Oxidationshemmer wie z.B. Mannit, Tocopherole oder Ascorbylpalmitat, oder ein thrombolytisches Enzym ist.

Revendications

Revendications pour les Etats contractants suivants : BE, DE, FR, GB, IT, LU, NL, SE

1. Emulsion d'hydrocarbure fluoré qui est stable après stérilisation à la chaleur et a une phase aqueuse continue, une phase discontinue comprenant un perfluorocarbone (autre qu'un perfluorocarbone bromé) en émulsion en une quantité de 50% poids/volume à 125% poids/volume, un agent émulsionnant et un moyen formant agent d'osmose mais non pas une association d'un phospholipide et d'un glycéride d'acides gras.

2. Emulsion d'hydrocarbure fluoré biocompatible pour une application à des corps d'animaux et à leurs organes, comprenant une phase aqueuse continue, une phase discontinue comprenant un hydrocarbure fluoré en émulsion en une quantité de 50% en poids par volume à 125% en poids par volume, un agent émulsionnant et un ou plusieurs moyens formant agent d'osmose pour maintenir l'osmolarité de l'émulsion, contenant une quantité efficace d'un alcool hexahydrique, d'un sucre, de chlorure de sodium, de bicarbonate de soude, de phosphate de potassium, de chlorure de calcium, de chlorure de magnésium, de sulfate de magnésium, d'imidazole, de tris(hydroxyméthyl)aminométhane, de phosphate monobasique de sodium ou de phosphate dibasique de sodium ou bien d'une association biocompatible ne précipitant pas le calcium, l'émulsion ne comprenant pas une association d'un phospholipide et d'un glycéride d'acides gras; à condition que quand l'hydrocarbure fluoré est un perfluorocarbone bromé, le moyen formant agent d'osmose ne se compose pas d'une association de phosphates de sodium et de glycérol.

3. Emulsion d'hydrocarbure fluoré selon la revendication 1 ou la revendication 2 où le moyen formant agent d'osmose contient un alcool hexahydrique.

4. Emulsion d'hydrocarbure fluoré selon la revendication 1, 2 ou 3, où l'agent émulsionnant comprend un phospholipide comme la lécithine et/ou un agent tensioactif anionique.

5. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1-4, où l'hydrocarbure fluoré est choisi parmi un perfluorocarbone monobromé, tel qu'un 1-bromoseptadécafluorooctane, un 1-bromotridécafluorohexane ou un 1-bromopentadécafluoroseptane, $C_4F_9CH\text{-}CHC_4F_9$ et la F-décaline.

6. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 5, où l'agent émulsionnant comprend un agent tensioactif fluoré biocompatible.

7. Emulsion d'hydrocarbure fluoré selon la revendication 6 où le co-agent tensioactif fluoré comprend un agent tensioactif polyhydroxylé fluoré.

8. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 7, comprenant de plus un agent tampon contenant de l'imidazole et/ou du tris(hydroxyméthyl)aminométhane.

9. Emulsion d'hydrocarbure fluoré selon la revendication 8 où le groupe de l'agent tampon comprend de plus du bicarbonate de soude, du phosphate monobasique de sodium, du phosphate dibasique de sodium, du sulfate de magnésium, du chlorure de magnésium, du chlorure de sodium, du chlorure de potassium, du phosphate monobasique de potassium ou du phosphate dibasique de potassium ou bien leur association ne précipitant pas le calcium.

10. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 9 où le pH de l'émulsion est maintenu entre 4,0 et 8,4, de préférence entre 7,0 et 7,8.

11. Emulsion d'hydrocarbure fluoré selon la revendication 8 où ledit agent tampon est l'imidazole et l'osmolarité de l'émulsion est maintenue entre 240 milliosmoles et 650 milliosmoles.

12. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 2 à 11, où l'alcool hexahydrique comme agent osmotique contient du mannitol.

13. Emulsion d'hydrocarbure fluoré selon la revendication 11, appropriée à une application à un tissu de corps d'animaux et/ou leurs organes, où le mannitol ajouté à l'émulsion l'est à raison de 0,25 gramme

à 1,5 grammes de mannitol pour 100 millilitres de l'émulsion.

14. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 13, qui comprend un anti-oxydant.

15. Emulsion d'hydrocarbure fluoré selon la revendication 14 où l'anti-oxydant comprend du mannitol, un tocophérol tel que l'acétate d'alpha-tocophérol, le palmitate d'ascorbyle et/ou l'imidazole.

16. Emulsion d'hydrocarbure fluoré selon la revendication 14 ou 15, où l'anti-oxydant comprend l'acide ascorbique, un sel ou son complexe ou son association ne précipitant pas le calcium.

17. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 16, où l'hydrocarbure fluoré en émulsion est en une quantité de 80% en poids par volume à 125% en poids par volume.

18. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 17 où le moyen pour maintenir l'osmolarité comprend du mannitol et l'osmolarité de l'émulsion est maintenue entre 240 milliosmoles et 650 milliosmoles.

19. Emulsion d'hydrocarbure fluoré selon la revendication 2 où le moyen formant agent d'osmose comprend au moins un sucre.

20. Emulsion d'hydrocarbure fluoré selon la revendication 19, où le sucre comprend du glucose, du mannose et/ou du fructose.

21. Emulsion d'hydrocarbure fluoré selon la revendication 2, 19 ou 20, où ledit moyen formant agent d'osmose contient de plus du mannitol et ledit sucre en une quantité efficace pour réduire la dégradation des globules rouges in vitro.

22. Emulsion d'hydrocarbure fluoré pour application à des corps d'animaux et leurs organes, comprenant une phase aqueuse continue, 50% à 125% en poids par volume d'un hydrocarbure fluoré et un agent émulsionnant et un moyen formant agent d'osmose pour maintenir l'osmolarité de l'émulsion dans le corps de l'animal et ses organes mais non pas une association d'un phospholipide et d'un glycéride d'acides gras, où le moyen formant agent d'osmose est caractérisé par l'un de ce qui suit :

(a) non glycérol et non salin;
(b) ne précipitant pas le calcium et approprié au maintien du pH de l'émulsion;
(c) non salin, non phosphaté et non glycérolé et approprié au maintien du pH de l'émulsion.

23. Méthode de préparation d'une émulsion d'hydrocarbure fluoré sensiblement stable après stérilisation et présentant 50% en poids par volume à 125% en poids par volume d'hydrocarbure fluoré en émulsion,comprenant les étapes de :

(a) préparer un véhicule pour la phase aqueuse en mélangeant, dans une quantité suffisante d'eau, un agent émulsionnant, une quantité effective d'un agent d'osmose;
(b) mélanger, dans le véhicule, à un taux mesuré, un hydrocarbure fluoré pour former un mélange;
(c) faire couler ledit mélange résultant selon au moins deux trajets d'écoulement;
(d) provoquer l'impact desdits deux trajets d'écoulement du mélange l'un dans l'autre dans une cavité à une pression supérieure à la pression atmosphérique;

l'émulsion ne comprenant pas une association d'un phospholipide et d'un glycéride d'acides gras, et à condition que quand l'hydrocarbure fluoré est un hydrocarbure fluoré bromé, le moyen formant agent d'osmose ne se compose pas d'une association de phosphates de sodium et de glycérol.

24. Méthode selon la revendication 23, où le véhicule contient de plus un agent tampon contenant de l'imidazole et/ou du tris(hydroxyméthyl)aminométhane.

25. Méthode selon la revendication 23 ou 24, où l'agent émulsionnant comprend de la lécithine, un agent tensioactif fluoré, ou un agent tensioactif anionique.

26. Méthode selon la revendication 23, 24 ou 25, où le mélange est forcé à s'écouler à 1500 pieds par seconde (460m/s) dans l'étape d'écoulement (c).

27. Méthode selon l'une quelconque des revendications 23 à 26, où la cavité est maintenue à 4000 livres par pouce au carré ($28MN/m^2$), et/ou la cavité a sa chaleur supprimée, par exemple en soumettant la cavité à un bain de glace, de préférence maintenu à 5 °C, à l'étape d'impact (d).

28. Méthode selon l'une quelconque des revendications 23 à 27,où l'étape d'écoulement et l'étape d'impact sont répétées, par exemple, quatre fois.

29. Méthode selon la revendication 28, comprenant de plus les étapes de recueillir le mélange après ladite étape d'impact et de stériliser ledit mélange par passage à l'autoclave.

30. Méthode selon l'une quelconque des revendications 23 à 29 où, dans le véhicule, l'agent d'osmose qui, de préférence, ne précipite pas le calcium, comprend un alcool hexahydrique comme le mannitol.

31. Méthode selon l'une quelconque des revendications 23 à 30, où l'hydrocarbure fluoré est choisi parmi un perfluorocarbone monobromé (tel que 1-bromoseptadécafluorooctane, 1-bromopentadécafluoroseptane ou 1-bromotridécafluorohexane), C_4F_9CH-CHC_4F_9, i-C_3F_7CH-CHC_6F_{13}, $C_6F_{13}CH=CHC_6F_{13}$ et F-adamantane, F-1, 3-dimethyladamantane, F-décaline, F-4-méthyloctahydroquinolidizine, F-4-méthyldécahydroquinoléine, F-4-cyclohexyl-pyrrolidine, F-2-butyltétrahydrofuranne, $(CF_3)_2CFO(CF_2CF_2)_20CF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)_30CF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)_2F$, $(CF_3)_2CFO(CF_2CF_2)_3F$, $(C_6F_{13})_{20}$,F-$[CF(CF_3)CF_{20}]_2CHFCF_3$ et leur association stable et compatible.

32. Utilisation d'une émulsion d'un hydrocarbure fluoré ayant une phase continue, une phase discontinue et une quantité mineure d'un agent émulsionnant formant une membrane entre les deux phases dans la préparation d'un système pour fourniture d'un médicament thérapeutique à un corps d'animal ou son organe.

33. Utilisation selon la revendication 32, où le médicament est soluble dans la phase discontinue de l'hydrocarbure fluoré ou est complexé avec la membrane formée par l'agent émulsionnant.

34. Utilisation selon la revendication 32 ou 33, où l'agent émulsionnant est la lécithine et le médicament est lipophile.

35. Utilisation selon la revendication 32, 33 ou 34, où le médicament est une enzyme comme la streptokinase, un antibiotique comme la céfoxitine, la gentamycine, la clindamycine et la rifampine, un protecteur hématopoiétique tel que l'imidazole ou son dérivé, un anti-oxydant comme le mannitol, les tocophérols ou le palmitate d'ascorbyle, ou bien une enzyme thrombolytique.

Revendications pour l'Etat contractant suivant : AT

1. Emulsion d'hydrocarbure fluoré qui est stable après stérilisation à la chaleur et a une phase aqueuse continue, et une phase discontinue comprenant un perfluorocarbone (autre qu'un perfluorocarbone bromé) en émulsion en une quantité de 50% poids/volume à 125% poids/volume un agent émulsionnant et un moyen formant agent d'osmose.

2. Emulsion d'hydrocarbure fluoré biocompatible pour une application à des corps d'animaux et à leurs organes comprenant une phase aqueuse continue, une phase discontinue comprenant un hydrocarbure fluoré en émulsion en une quantité de 50% en poids par volume à 125% en poids par volume, un agent émulsionnant et un ou plusieurs moyens formant agent d'osmose pour maintenir l'osmolarité de l'émulsion contenant une quantité efficace d'un alcool hexahydrique, d'un sucre, de chlorure de sodium, de bicarbonate de soude, de phosphate de potassium, de chlorure de calcium, de chlorure de magnésium, de sulfate de magnésium, d'imidazole, de tris(hydroxyméthyl)aminométhane, de phosphate monobasique de sodium ou de phosphate dibasique de sodium ou bien d'une association biocompatible ne précipitant pas le calcium; à condition que quand l'hydrocarbure fluoré est un perfluorocarbone chromé, le moyen formant agent d'osmose ne se compose pas d'une association de sulfate de sodium et de glycérol.

3. Emulsion d'hydrocarbure fluoré selon la revendication 1 ou la revendication 2 où le moyen formant agent d'osmose contient un alcool hexahydrique.

4. Emulsion d'hydrocarbure fluoré selon la revendication 1, 2 ou 3, où l'agent émulsionnant comprend un phospholipide comme la lécithine et/ou un agent tensioactif anionique.

5. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1-4, où l'hydrocarbure fluoré est choisi parmi un perfluorocarbone monobromé, tel qu'un bromoseptadécafluorooctane, un 1-bromotridécafluorohexane ou un 1-bromopentadécafluoroseptane, $C_4F_9CH\text{-}CHC_4F_9$ et la F-décaline.

6. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 5, où l'agent émulsionnant comprend un agent tensioactif fluoré biocompatible.

7. Emulsion d'hydrocarbure fluoré selon la revendication 6 où le co-agent tensioactif fluoré comprend un agent tensioactif polyhydroxylé fluoré.

8. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 7, comprenant de plus un agent tamponnant contenant de l'imidazole et/ou du tris(hydroxyméthyl)aminométhane.

9. Emulsion d'hydrocarbure fluoré selon la revendication 8 où le groupe de l'agent tampon comprend de plus du bicarbonate de soude, du phosphate monobasique de sodium, du phosphate dibasique de sodium, du sulfate de magnésium, du chlorure de magnésium, du chlorure de sodium, du chlorure de potassium, du phosphate monobasique de potassium ou du phosphate dibasique de potassium ou bien leur association ne précipitant pas le calcium.

10. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 9 où le pH de l'émulsion est maintenu entre 4,0 et 8,4, de préférence entre 7,0 et 7,8.

11. Emulsion d'hydrocarbure fluoré selon la revendication 8 où ledit agent tampon est l'imidazole et l'osmolarité de l'émulsion est maintenue entre 240 milliosmoles et 650 milliosmoles.

12. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 2 à 11, où l'alcool hexahydrique comme agent osmotique contient du mannitol.

13. Emulsion d'hydrocarbure fluoré selon la revendication 11, appropriée à une application, à un tissu de corps d'animaux et/ou leurs organes, ou le mannitol ajouté à l'émulsion l'est à raison de 0,25 gramme à 1,5 grammes de mannitol pour 100 millilitres de l'émulsion.

14. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 13, qui comprend un anti-oxydant.

15. Emulsion d'hydrocarbure fluoré selon la revendication 14 où l'anti-oxydant comprend du mannitol, un tocophérol tel que l'acétate d'alpha-tocophérol, le palmitate d'ascorbyle et/ou l'imidazole.

16. Emulsion d'hydrocarbure fluoré selon la revendication 14 ou 15, où l'anti-oxydant comprend l'acide ascorbique, un sel ou son complexe ou son association ne précipitant pas le calcium.

17. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 16, où l'hydrocarbure fluoré en émulsion est en une quantité de 80% en poids par volume à 125% en poids par volume.

18. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 17 où le moyen pour maintenir l'osmolarité comprend du mannitol et l'osmolarité de l'émulsion est maintenue entre 240 milliosmoles et 650 milliosmoles.

19. Emulsion d'hydrocarbure fluoré selon la revendication 2 où le moyen formant agent d'osmose comprend au moins un sucre.

20. Emulsion d'hydrocarbure fluoré selon la revendication 19, où le sucre comprend du glucose, du mannose et/ou du fructose.

21. Emulsion d'hydrocarbure fluoré selon la revendication 2, 19 ou 20, où ledit moyen formant agent d'osmose contient de plus du mannitol et ledit sucre en une quantité efficace pour réduire la dégradation des globules rouges in vitro.

22. Emulsion d'hydrocarbure fluoré pour application à des corps d'animaux et leurs organes comprenant une phase aqueuse continue, 50% à 125% en poids par volume d'un hydrocarbure fluoré et un agent émulsionnant et un moyen formant agent d'osmose pour maintenir l'osmolarité de l'émulsion dans le corps de l'animal et ses organes mais non pas une association d'un phospholipide et d'un glycéride d'acides gras, où le moyen formant agent d'osmose est caractérisé par l'un de ce qui suit :
(a) non glycérol et non salin;
(b) ne précipitant pas le calcium et approprié au maintien du pH de l'émulsion;
(c) non salin, non phosphaté et non glycérolé et approprié au maintien du pH de l'émulsion.

23. Méthode de préparation d'une émulsion d'hydrocarbure fluoré sensiblement stable après stérilisation et présentant 50% en poids par volume à 125% en poids par volume d'hydrocarbure fluoré en émulsion,comprenant les étapes de :
(a) préparer un véhicule pour la phase aqueuse en mélangeant, dans une quantité suffisante d'eau, un agent émulsionnant, une quantité effective d'un agent d'osmose;
(b) mélanger, dans le véhicule, à un taux mesuré, un hydrocarbure fluoré pour former un mélange;
(c) faire couler ledit mélange résultant selon au moins deux trajets d'écoulement;
(d) provoquer l'impact desdits deux trajets d'écoulement du mélange l'un dans l'autre dans une cavité à une pression supérieure à la pression atmosphérique;
à condition que, quand l'hydrocarbure fluoré est un hydrocarbure fluoré bromé, le moyen formant agent d'osmose ne se compose pas d'une association de phosphates de sodium et de glycérol.

24. Méthode selon la revendication 23, où le véhicule contient de plus un agent tamponnant contenant de l'imidazole et/ou du tris(hydroxyméthyl)aminométhane.

25. Méthode selon la revendication 23 ou 24, où l'agent émulsionnant comprend de la lécithine, un agent tensioactif fluoré, ou un agent tensioactif anionique.

26. Méthode selon la revendication 23, 24 ou 25, où le mélange est forcé à s'écouler à 1500 pieds par seconde (460m/s) dans l'étape d'écoulement (c).

27. Méthode selon l'une quelconque des revendications 23 à 26, où la cavité est maintenue à 4000 livres par pouce au carré (28MN/m^2), et/ou la cavité a sa chaleur supprimée par exemple en soumettant la cavité à un bain de glace, de préférence maintenu à 5 • C, à l'étape d'impact (d).

28. Méthode selon l'une quelconque des revendications 23 à 27,où l'étape d'écoulement et l'étape d'impact sont répétées, par exemple, quatre fois.

29. Méthode selon la revendication 28, comprenant de plus les étapes de recueillir le mélange après ladite étape d'impact et de stériliser ledit mélange par passage à l'autoclave.

30. Méthode selon l'une quelconque des revendications 23 à 29 où, dans le véhicule, l'agent d'osmose qui, de préférence, ne précipite pas le calcium, comprend un alcool hexahydrique comme le mannitol.

31. Méthode selon l'une quelconque des revendications 23 à 30, où l'hydrocarbure fluoré est choisi parmi un perfluorocarbone monobromé (tel que 1-bromoseptadécafluorooctane, 1-bromopentadécafluoroseptane ou 1-bromotridécafluorohexane), C_4F_9CH-CHC_4F_9, i-C_3F_7CH-CHC_6F_{13}, $C_6F_{13}CH=CHC_6F_{13}$ et F-adamantane, F-1, 3-dimethyladamantane, F-décaline, F-4-méthyloctahydroquinolidizine, F-4-méthyldécahydroquinoléine, F-4-cyclohexyl-pyrrolidine, F-2-butyltétrahydrofuranne, $(CF_3)_2CFO(CF_2CF_2)_20CF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)_30CF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)_2F$, $(CF_3)_2CFO(CF_2CF_2)_3F$, $(C_6F_{13})_20$,F-$[CF(CF_3)CF_20]_2CHFCF_3$ et leur association stable et compatible.

32. Utilisation d'une émulsion d'un hydrocarbure fluoré ayant une phase continue, une phase discontinue et une quantité mineure d'un agent émulsionnant formant une membrane entre les deux phases dans la préparation d'un système pour fourniture d'un médicament thérapeutique à un corps d'animal ou son

organe.

33. Utilisation selon la revendication 32, où le médicament est soluble dans la phase discontinue de l'hydrocarbure fluoré ou est complexé avec la membrane formée par l'agent émulsionnant.

34. Utilisation selon la revendication 32 ou 33, où l'agent émulsionnant est la lécithine et le médicament est lipophile.

35. Utilisation selon la revendication 32, 33 ou 34, où le médicament est une enzyme comme la streptokinase, un antibiotique comme la céfoxitine, la gentamycine, la clindamycine et la rifampine, un protecteur hématopoiétique tel que l'imidazole ou son dérivé, un anti-oxydant comme le mannitol, les tocophérols ou le palmitate d'ascorbyle, ou bien une enzyme thrombolytique.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'une émulsion d'hydrocarbure fluoré qui est sensiblement stable après stérilisation à la chaleur, le procédé consistant à mélanger un composant en phase aqueuse continue, un composant en phase discontinue comprenant un perfluorocarbone (autre qu'un perfluorocarbone bromé) en émulsion en une quantité de 50% poids/volume à 125% poids/volume, un agent émulsionnant et un moyen formant agent d'osmose mais non pas une association d'un phospholipide et d'un glycéride d'acides gras.

2. Procédé pour la préparation d'une émulsion d'hydrocarbure fluoré biocompatible pour application à des corps d'animaux et leurs organes, le procédé consistant à mélanger une phase aqueuse continue, une phase discontinue comprenant un hydrocarbure fluoré en émulsion en une quantité de 50% en poids par volume à 125% en poids par volume, un agent émulsionnant et un ou plusieurs moyens formant agent d'osmose pour maintenir l'osmolarité de l'émulsion, contenant une quantité efficace d'un alcool hexahydrique, d'un sucre, de chlorure de sodium, de bicarbonate de soude, de phosphate de potassium, de chlorure de calcium, de chlorure de magnésium, de sulfate de magnésium, d'imidazole, de tris(hydroxyméthyl)aminométhane, de phosphate monobasique de sodium ou de phosphate dibasique de sodium ou bien d'une association biocompatible ne précipitant pas le calcium, l'émulsion ne comprenant pas une association d'un phospholipide et d'un glycéride d'acides gras; à condition que quand l'hydrocarbure fluoré est un perfluorocarbone bromé, le moyen formant agent d'osmose ne se compose pas d'une association de phosphates de sodium et de glycérol.

3. Procédé selon la revendication 1 ou 2, où le moyen formant agent d'osmose comporte un alcool hexahydrique.

4. Procédé selon la revendication, 1, 2 ou 3 où l'agent émulsionnant comprend un phospholipide tel que la lécithine et/ou un agent tensioactif anionique.

5. Procédé selon l'une quelconque des revendications 1 à 4, où l'hydrocarbure fluoré est choisi parmi un perfluorocarbone monobromé, tel qu'un 1-bromoseptadécafluorooctane, un 1-bromotridécafluorohexane ou un 1-bromopentadécafluoroseptane, $C_4F_9CH\text{-}CHC_4F_9$ et la F-décaline.

6. Procédé selon l'une quelconque des revendications 1 à 5, où l'agent émulsionnant comprend un agent tensioactif fluoré biocompatible.

7. Procédé selon la revendication 6, où le co-agent tensioactif fluoré se compose d'un agent tensioactif polyhydroxylé fluoré.

8. Procédé selon l'une quelconque des revendications 1 à 7, comprenant de plus un agent tampon comprenant de l'imidazole et/ou du tris(hydroxyméthyl) aminométhane.

9. Procédé selon la revendication 8, où le groupe de l'agent tampon contient de plus du bicarbonate de soude, du phosphate monobasique de sodium, du phosphate dibasique de sodium, du sulfate de magnésium, du chlorure de magnésium, du chlorure de sodium, du chlorure de potassium, du phosphate monobasique de potassium ou du phosphate dibasique de potassium ou bien leur associa-

tion ne précipitant pas le calcium.

10. Procédé selon l'une quelconque des revendications 1 à 9, où le pH de l'émulsion est maintenu entre 4,0 et 8,4 et de préférence entre 7,0 et 7,8.

11. Procédé selon la revendication 8, où ledit agent tampon est l'imidazole et l'osmolarité de l'émulsion est maintenu entre 240 milliosmoles et 650 milliosmoles.

12. Procédé selon l'une quelconque des revendications 2 à 11, où l'alcool hexahydrique comme agent d'osmose comprend du mannitol.

13. Procédé selon la revendication 11, approprié à une application à un tissu de corps d'animaux et/ou leurs organes, où le mannitol ajouté à l'émulsion est compris entre 0,25 gramme et 1,5 grammes de mannitol pour 100 millitres de l'émulsion.

14. Procédé selon l'une quelconque des revendications 1 à 13, qui comprend un anti-oxydant.

15. Procédé selon la revendication 14, où l'anti-oxydant comprend du mannitol, un tocophérol tel que l'acétate d'alpha-tocophérol, le palmitate d'ascorbyle et/ou l'imidazole.

16. Emulsion d'hydrocarbure fluoré selon la revendication 14 ou 15, où l'anti-oxydant comprend l'acide ascorbique, un sel ou son complexe ou son association ne précipitant pas le calcium.

17. Emulsion d'hydrocarbure fluoré selon l'une quelconque des revendications 1 à 16, où l'hydrocarbure fluoré en émulsion est en une quantité de 80% en poids par volume à 125% en poids par volume.

18. Procédé selon l'une quelconque des revendications 1 à 17 où le moyen pour maintenir l'osmolarité comprend du mannitol et l'osmolarité de l'émulsion est maintenue entre 240 milliosmols et 650 milliosmols.

19. Procédé selon la revendication 2, où le moyen formant agent d'osmose comprend au moins un sucre.

20. Procédé selon la revendication 19, où le sucre comprend du glucose, du mannose et/ou du fructose.

21. Procédé selon la revendication 2, 19 ou 20, où ledit moyen formant agent d'osmose contient de plus du mannitol et ledit sucre en une quantité efficace pour réduire la dégradation des globules rouges du sang in vitro.

22. Emulsion d'hydrocarbure fluoré pour application à des corps d'animaux et leurs organes, comprenant une phase aqueuse continue, 50% à 125% en poids par volume d'un hydrocarbure fluoré et un agent émulsionnant et un moyen formant agent d'osmose pour maintenir l'osmolarité de l'émulsion dans le corps de l'animal et ses organes mais non pas une association d'un phospholipide et d'un glycéride d'acides gras, où le moyen formant agent d'osmose est caractérisé par l'un de ce qui suit :
    (a) non glycérol et non salin;
    (b) ne précipitant pas le calcium et approprié au maintien du pH de l'émulsion;
    (c) non salin, non phosphaté et non glycérolé et approprié au maintien du pH de l'émulsion.

23. Méthode de préparation d'une émulsion d'hydrocarbure fluoré sensiblement stable après stérilisation et présentant 50% en poids par volume à 125% en poids par volume d'hydrocarbure fluoré en émulsion,comprenant les étapes de :
    (a) préparer un véhicule pour la phase aqueuse en mélangeant, dans une quantité suffisante d'eau, un agent émulsionnant, une quantité effective d'un agent d'osmose;
    (b) mélanger, dans le véhicule à un taux mesuré, un hydrocarbure fluoré pour former un mélange;
    (c) faire couler ledit mélange résultant selon au moins deux trajets d'écoulement;
    (d) provoquer l'impact desdits deux trajets d'écoulement du mélange l'un dans l'autre dans une cavité à une pression supérieure à la pression atmosphérique;
    l'émulsion ne comprenant pas une association d'un phospholipide et d'un glycéride d'acides gras, et à condition que quand l'hydrocarbure fluoré est un hydrocarbure fluoré bromé, le moyen formant agent

d'osmose ne se compose pas d'une association de phosphates de sodium et de glycérol.

24. Méthode selon la revendication 23, où le véhicule contient de plus un agent tampon contenant de l'imidazole et/ou du tris(hydroxyméthyl)aminométhane.

25. Méthode selon la revendication 23 ou 24, où l'agent émulsionnant comprend de la lécithine, un agent tensioactif fluoré, ou un agent tensioactif anionique.

26. Méthode selon la revendication 23, 24 ou 25, où le mélange est forcé à s'écouler à 1500 pieds par seconde (460m/s) dans l'étape d'écoulement (c).

27. Méthode selon l'une quelconque des revendications 23 à 26, où la cavité est maintenue à 4000 livres par pouce au carré (28MN/m^2), et/ou la cavité a sa chaleur supprimée, par exemple en soumettant la cavité à un bain de glace, de préférence maintenu à 5 • C, à l'étape d'impact (d).

28. Méthode selon l'une quelconque des revendications 23 à 27,où l'étape d'écoulement et l'étape d'impact sont répétées, par exemple, quatre fois.

29. Méthode selon la revendication 28, comprenant de plus les étapes de recueillir le mélange après ladite étape d'impact et de stériliser ledit mélange par passage à l'autoclave.

30. Méthode selon l'une quelconque des revendications 23 à 29 où, dans le véhicule, l'agent d'osmose qui de préférence, ne précipite pas le calcium, comprend un alcool hexahydrique comme le mannitol.

31. Méthode selon l'une quelconque des revendications 23 à 30, où l'hydrocarbure fluoré est choisi parmi un perfluorocarbone monobromé (tel que 1-bromoseptadécafluorooctane, 1-bromopentadécafluoroseptane ou 1-bromotridécafluorohexane), $C_4F_9CH\text{-}CHC_4F_9$, $i\text{-}C_3F_7CH\text{-}CHC_6F_{13}$, $C_6F_{13}CH=CHC_6F_{13}$ et F-adamantane, F-1, 3-dimethyladamantane, F-décaline, F-4-méthyloctahydroquinolidizine, F-4-méthyldécahydroquinoléine, F-4-cyclohexyl-pyrrolidine, F-2-butyltétrahydrofuranne, $(CF_3)_2CFO(CF_2CF_2)_20CF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)_30CF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)_2F$, $(CF_3)_2CFO(CF_2CF_2)_3F$, $(C_6F_{13})_20$,F-$[CF(CF_3)CF_20]_2CHFCF_3$ et leur association stable et compatible.

32. Utilisation d'une émulsion d'un hydrocarbure fluoré ayant une phase continue, une phase discontinue et une quantité mineure d'un agent émulsionnant formant une membrane entre les deux phases dans la préparation d'un système pour fourniture d'un médicament thérapeutique à un corps d'animal ou son organe.

33. Utilisation selon la revendication 32, où le médicament est soluble dans la phase discontinue de l'hydrocarbure fluoré ou est complexé avec la membrane formée par l'agent émulsionnant.

34. Utilisation selon la revendication 32 ou 33, où l'agent émulsionnant est la lécithine et le médicament est lipophile.

35. Utilisation selon la revendication 32, 33 ou 34, où le médicament est une enzyme comme la streptokinase, un antibiotique comme la céfoxitine, la gentamycine, la clindamycine et la rifampine, un protecteur hématopoiétique tel que l'imidazole ou son dérivé, un anti-oxydant comme le mannitol, les tocophérols ou le palmitate d'ascorbyle, ou bien une enzyme thrombolytique.